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VALUE OF QUANTITATIVE OLFACTORY TESTS FOR LOCALIZATION OF SUPRATENTORIAL DISEASE

ANALYSIS OF ONE THOUSAND CASES

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In 1935 one of us (C. A. E.) and associates [1] described a new procedure for examination of the olfactory sense by the blast injection and stream injection of odorous substances into the nasal passages. The method of blast injection was based on a new principle. We found in normal subjects, by the introduction of odorous substances into the nasal passages during periods of voluntary cessation of breathing, in known volume and under a known pressure, that a certain volume and pressure were necessary for the recognition and identification of the odor. The minimum volume required for the identification of the odor was called the minimum identifiable odor of the odorous substance. Furthermore, we found that the stream injection of an odorous substance for a fixed period produced olfactory fatigue—inability to identify the odor when injected into the nasal passage by blast injection—from which normal subjects recovered within a definite number of minutes. These quantitative tests were recommended for the examination of the olfactory sense. All those who have published papers on the use of the method (Adler

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1. Elsberg, C. A., and Levy, I.: A New and Simple Method of Quantitative Olfactometry, Bull. Neurol. Inst. New York **4**:5-19, 1935. Elsberg, C. A.; Brewer, E. D., and Levy, I.: The Odorous Substances to Be Used for Tests of the Olfactory Sense, ibid. **4**:286-293, 1935; The Relative Importance of Volume and Pressure of the Impulse for the Sensation of Smell, and the Nature of the Olfactory Process, ibid. **4**:264-269, 1935.

and Finley,[2] Echols and associates,[3] Spillane[4] and others) have confirmed the statement made by us, namely, that the procedure is a reliable quantitative method for testing the sense of smell in normal persons.

In a further series of papers[5] one of us (Elsberg) and Stewart suggested that these quantitative olfactory tests are of value for the localization of tumors and other diseases of the brain. Some investigators who have employed the test for this purpose did not obtain the same results as those described by us. Later in this paper we shall suggest the explanation for the divergent results they obtained.

METHOD

The technic of the method has been described in many papers and will not be given in detail here. Some improvement has been made in the apparatus by the attachment of a small solenoid valve to the test bottle, so that the release of the odorous substance from the bottle into the nasal passage is made electrically at a constant rate. The solenoid valve is an improvement but is not necessary.

The results described in this report are based on observations with two odorous substances—coffee and citral—and were considered definite only when the blast and the stream injections of both substances showed similar abnormalities. These two odorous substances were selected because their odors are familiar and easily recognized. Other substances might serve equally well.

The most important part of the technic of the test is the exact determination of the minimal identifiable odor on each side of the nose; therefore extreme care must be taken to find the smallest volume and pressure of the blast injection necessary for the recognition and identification of the odor. If the value erroneously obtained is too high, the duration of fatigue (after the stream injection) will be within normal limits, for it is determined by the time that is required before the subject will again be able to identify the odorous substance when he receives blast injections of the substance at the previously determined value for the minimal identifiable odor. This appears to have been the technical error made by Adler and Finley,[2] who were unable to obtain any prolongation of fatigue in their patients with tumors of the brain. On the other hand, if the value obtained is too low, which is rarely the case, the duration of the fatigue produced by stream injection of the odor will appear prolonged beyond the normal limits.

On the basis of experience in tests on a large series of normal subjects, we have arrived at the conclusion that the normal value for the minimal identifiable

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2. Adler, A., and Finley, K. H.: Clinical Results with Elsberg's Olfactory Test, Arch. Neurol. & Psychiat. **40**:147 (July) 1938.

3. Echols, D. H.; Richter, H. J., and Peet, M. M.: The Effect of Zinc Sulphate on the Sense of Smell, Bull. Univ. Hosp., Ann Arbor **3**:32-33, 1937.

4. Spillane, J. D.: Clinical Investigations of Olfactory Function in Brain Tumor Patients, Brain **62**:213-221, 1939.

5. Elsberg, C. A.: The Value of Quantitative Olfactory Tests for the Localization of Supratentorial Tumors of the Brain, Bull. Neurol. Inst. New York **4**:511-522, 1935; The Localization of Supratentorial Tumors of the Brain by Olfactory Tests, Ann. Int. Med. **10**:49-57, 1936; The Localization of Tumors of the Frontal Lobes of the Brain by Quantitative Olfactory Tests, Bull. Neurol. Inst. New York **4**:535-543, 1936. Elsberg, C., and Stewart, J.: Quantitative Olfactory Tests: Value in Localization and Diagnosis of Tumors of the Brain, Arch. Neurol. & Psychiat. **40**:471-481 (Sept.) 1938.

odor for the coffee we used is between 5 and 10 cc. and that that for citral is between 3 and 9 cc. After a stream injection of coffee for thirty seconds, the duration of the refractory period is between thirty seconds and four minutes; after a stream injection of citral for thirty seconds, the duration of the refractory period for citral is between thirty seconds and four and a half minutes.

The effect of pressure on the external olfactory pathways (olfactory nerves, bulbs and tracts; external and internal olfactory roots) is to cause an elevation of the value for the minimal identifiable odor above the values given for normal subjects. Elevation of the value for the minimal identifiable odor on one or both sides is therefore an evidence of pressure on or involvement of one or both external olfactory pathways.

Interference with the functions of the internal olfactory pathways (within the substance of the cerebral hemispheres) causes prolongation of olfactory fatigue, i. e., of the refractory period during which the patient is unable to identify the odor. This fatigue is ipsilateral; that is, if there is a lesion in one cerebral hemisphere, olfactory fatigue is prolonged beyond what is normal after a stream injection of the odorous substance into the nasal passage on the same side as the cerebral lesion.

Finally, mention must be made of the fact that these tests of olfactory function require considerable cooperation on the part of the patient. Of the 1,000 patients results for whom form the basis of this report, the number whose cooperation was poor or questionable is shown in the following tabulation:

	Number of Subjects
Cooperation poor	42
Cooperation questionable	85

In addition, there were 28 patients on whom the tests could not be made because they would not cooperate at all. Therefore 155 patients (15.5 per cent) either would not cooperate at all, so that quantitative tests could not be made, or cooperated so poorly or to so questionable a degree that the results were not absolutely reliable. Notwithstanding this fact, the 126 subjects whose cooperation was poor or questionable are included with the 1,000 patients results for whom are analyzed in this report.

RESULTS

The results of quantitative olfactory tests on 1,000 patients are analyzed in this paper.[6] In the majority of instances the patients were suffering from suspected or verified intracranial disease, as shown in table 1.

Patients in Whom There Was No Evidence of Disturbed Olfactory Function.—In 341 subjects (34.1 per cent) the values for the minimal identifiable odor and the duration of fatigue were within normal limits. Data on these subjects are summarized in table 2.

In 257 of these patients, either there was no definite evidence of an organic intracranial lesion, or the lesion was diffuse or subtentorial. In these patients the function of the olfactory pathways might actually have been undisturbed. There remained, therefore, 84 patients with localized intracranial lesions in whom the olfactory tests failed to show a distur-

6. Most of the tests were made by Miss G. Vetter.

bance of the extracerebral or the intracerebral olfactory pathways. Furthermore, among these 84 subjects there were 19 with pituitary tumor in whom the growth appeared to be confined within the sella turcica

TABLE 1.—*Distribution of Disease in a Series of One Thousand Patients*

	No. of Patients
Supratentorial tumor of the brain, verified	193
Supratentorial tumor of the brain, suspected	45
Infratentorial tumor of the brain	35
Pituitary tumor	54
Aneurysm of cerebral artery	15
Thrombosis of cerebral artery	24
Subdural hematoma	7
Encephalitis, acute	7
Encephalitis, chronic	20
Encephalopathy, post-traumatic	34
Cerebral arteriosclerosis	31
Cerebral atrophy	24
Grand mal and petit mal	157
Encephalomyelitis	7
Meningitis, chronic or subacute	13
Migraine; headache from unknown cause	22
Multiple sclerosis	24
Hysteria, psychoneuroses, etc.	119
Trigeminal neuralgia	11
Ménière's syndrome	13
Neuritis of cranial nerve(s)	21
Cerebrospinal syphilis	14
Chiasmal arachnoiditis	3
Chronic hydrocephalus	4
Porencephaly	6
Brain abscess	3
Diseases of the spinal cord	39
Myasthenia gravis	6
Sinusitis	7
Varia	42
Total	1,000

TABLE 2.—*Analysis of Cases of Disease with Normal Olfactory Function*

	Total Number of Cases in Series	Cases with Normal Olfactory Function	
		Number	Percentage *
Supratentorial tumor of brain	193	29	15
Infratentorial tumor of brain	35	14	40
Pituitary tumor	54	19	17
Encephalopathy	34	19	56
Encephalitis	27	9	33
Serous meningitis	13	4	31
Neuritis of cranial nerves	21	8	38
Cerebral thrombosis	24	7	29
Multiple sclerosis	24	14	58
Grand mal and petit mal	157	58	37
Migraine, headache from unknown cause	22	12	55
Aneurysm of cerebral artery	15	4	27
Diseases of the spinal cord	39	10	26
Hysteria; psychoneuroses, etc.	119	31	25
Varia	...	103	
Total		341	

* The percentages show that normal olfactory function was much more rare with supratentorial tumors of the brain and pituitary tumors than with any other disturbance.

beneath the sellar diaphragm (absence of neighborhood signs, i. e., disturbances of the visual fields). In the remaining 65 patients the lesion must have involved a definite part of the cerebral hemispheres or of the extracerebral pathways (olfactory nerves, bulbs or tracts,

olfactory roots), but there was no evidence that the functions of the extracerebral or intracerebral olfactory pathways had been disturbed.

Significance of Complete Anosmia.—By complete anosmia is meant the inability, not due to obstruction or other gross lesion in the nasal passages, to recognize and identify any of the test odors either when the substance is inhaled or when it is given by blast injection.

Of the 1,000 patients, 77, or 7.7 per cent, had complete anosmia. There was complete loss of the sense of smell in 23 of 193 patients with verified supratentorial tumors of the brain (12 per cent of the patients with tumor) and in 54 of the remaining 807 patients (6.7 per cent).

As fracture of the skull and other injuries to the head may be the cause of the loss of the sense of smell, it seemed of interest to investigate the relation of cranial trauma to the frequency of anosmia. Of the 77 patients with anosmia, there was history of preceding injury to the head in 32 (42 per cent). There was a history of cranial trauma in 4[7] of 23 patients (17 per cent) with supratentorial tumor of the brain and anosmia and in 12[8] of the 54 patients (22 per cent) with other diseases. Of the 1,000 patients, anosmia with a history of trauma to the head occurred in 16 (1.6 per cent)—in 4 of 193 patients (2.1 per cent) with verified supratentorial tumor and in 12 of 807 patients (1.5 per cent) who

TABLE 3.—*Situation of Tumor in Twenty-Three Patients with Brain Tumor and Anosmia*

Olfactory groove	5
Sphenoid ridge	5
Frontal, frontotemporal or temporal	11
Parietal or occipital	2

were suffering from other conditions. As was to be expected, the incidence of trauma was about the same in the three groups.

Of the 23 patients with supratentorial tumor and anosmia, anosmia was of no little significance for the localization of the growth, as shown in table 3.

Therefore, if a patient with a supratentorial tumor of the brain has complete loss of the sense of smell the probability is 91 per cent that the tumor is frontal, temporal or temporofrontal. If there is no history of preceding cranial trauma the probability is higher.

In the majority of instances the localization of intracranial lesions by quantitative olfactory tests is based on the combined results of the determination of elevations of values for the minimal identifiable odor and of abnormally prolonged duration of olfactory fatigue.

In order that the reader may gain an idea of the relative significance of each of these factors, the results of tests from the standpoint of the

7. In 2 of the subjects the trauma to the head was of slight degree, while in the other 2 it was severe, with loss of consciousness for at least several hours.

8. In 5 of these patients the trauma was of slight degree, and in the remaining 7 it was severe, with loss of consciousness.

minimal identifiable odor alone and of prolongation of fatigue alone are given in the following sections. The results appear to show that the tests have most value when both the minimal identifiable odor and fatigue are taken into account.

Significance of Unilateral or Bilateral Elevation of Values for the Minimal Identifiable Odor.—Analysis of the olfactory records of the patients from the standpoint of elevation of the value for the minimal identifiable odor alone gave the following results: There were 239 patients in whom unilateral or bilateral elevation of the value for the minimal identifiable odor was interpreted as evidence of a lesion in or around the frontal lobe of the brain. In 111 of the 239 patients either the cerebral lesion was diffuse or a clinical diagnosis of the location of the lesion could not be made. In these patients the external olfactory pathways may or may not have been involved. Conclusions regarding the value of the tests can be drawn only when the location of the lesion

TABLE 4.—*Results of Olfactory Tests for Minimal Identifiable Odor Alone on Two Hundred and Thirty-Nine Patients with Elevation Above Normal of Values for the Minimal Identifiable Odor*

	Entire Series of 239 Patients		Patients (177) with No History of Trauma	
	Number	Percentage	Number	Percentage
Correctly localized in or around frontal or temporal lobes	91	38	79	45
Localization in doubt	10	..	2	1
Incorrectly localized	5	2	..	..
Diffuse disease or situation not known	111	..	76	..
No evidence of an intracranial lesion	22	..	20	..

is certain. Therefore, there remain for analysis the results for 128 patients. In 91, or 71 per cent of these, the value for the minimal identifiable odor correctly indicated that the lesion was in or around the frontal lobe or an adjoining portion of the temporal lobe. In 5 patients (4 per cent) the olfactory localization was incorrect; in 10 (8 per cent) the localization was in doubt, and in 22 (16 per cent) there was no clinical evidence of an intracranial lesion.

Therefore, if a patient with the symptoms of a supratentorial lesion has unilateral or bilateral elevation above the normal of values for the minimal identifiable odor, the probability is 71 per cent that the lesion is on or around the frontal or the temporal lobe of the brain.

However, a complete study of our materials must include an analysis of the results of the tests for the minimal identifiable odor for all of the 239 patients with elevation of values for this factor. In the analysis, it may be of interest to divide the subjects into two groups, those with and those without a history of a preceding cranial trauma. There were

62 patients who gave a history of having sustained an injury to the head [9] and 177 who declared that they had never been so injured.

Therefore, if unilateral or bilateral elevation of values for the minimal identifiable odor is found by the blast injection tests, the probability is between 38 and 45 per cent that the lesion is frontal, temporal or fronto-temporal. If diffuse and unlocalized diseases are excluded, the probability is between 71 and 78 per cent that the lesion is in or around the frontal or the temporal lobe.

Significance of Olfactory Tests for Prolonged Fatigue Alone.—The results in table 5 show that on the basis of prolongation of fatigue alone, correct localization was made in 70 patients, or 54 per cent.

As we have already stated, in the majority of instances the localization of intracranial lesions by the quantitative olfactory tests is based not

TABLE 5.—*Results of Olfactory Tests for Prolongation of Fatigue Alone on One Hundred and Twenty-Nine Patients with Verified or Certain Supratentorial Lesions*

	Localization						No Localization		Localization to One Side	
	Correct		Incorrect		In Doubt					
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Localized lesions.....	43	65	11	17	..	..	12	18	..	..
Diffuse lesions *.....	27	42	..	..	12	19	..	..	24	39

* In 61 cases the diagnosis was in doubt or it was uncertain whether the disease was localized or diffuse.

alone on determinations of abnormally prolonged duration of olfactory fatigue but on the combination of the two procedures. In what follows, we shall give (1) the results of complete olfactory tests on all the patients in our series and (2) the results of complete tests on patients with tumors of the brain and some other intracranial disturbances.

Localization of Lesion by Complete Olfactory Tests in Entire Series.—Exclusive of the 77 patients with anosmia on whom quantitative olfactory tests could not be made, 35 patients with infratentorial lesions and 92 patients for whom, for one reason or another, the tests were incomplete, the results for the series are shown in table 6.

(*a*) In 103 of 251 patients with verified lesions (41 per cent) the localization was correct as regards both lobe and side or as regards the lobe or the side; in 13 patients (5 per cent) the olfactory localization was

9. In 44, the cranial trauma was slight; in 18, severe with loss of consciousness.

incorrect, and in 115 patients (42 per cent) no olfactory evidence of a localized lesion was found.

(*b*) Of 221 patients with diffuse intracranial lesions, the olfactory tests correctly indicated a diffuse lesion in 52 (24 per cent), the tests were interpreted as indicating a lesion on one side of the brain in 87 (39 per cent) and there was no evidence of a localized disease in 82 (37 per cent).

(*c*) Of 324 patients with various conditions (unlocalized lesions; hysteria; psychoneuroses, etc.) or with no evidence of an intracranial lesion, the olfactory tests indicated a localized lesion in 95 (29 per cent) and a diffuse lesion in 10 (3 per cent), and gave no evidence of localization in 219 (68 per cent).

In 22 patients for whom the clinical diagnosis was "deferred" but in whom there were definite clinical signs of involvement of one or the

TABLE 6.—*Localization by Complete Olfactory Tests in Seven Hundred Ninety-Six Patients*

Clinical Diagnosis	Correctly Localized	Localized Only as to Lobe	Localized Only as to Side	Incorrectly Localized	Interpreted as Diffuse Lesion	Not Localized	Localized to One Side	Total
Localized lesion	75	16	12	13	20	115	..	251
Diffuse lesion	52	..	..	..	52	82	87	221
Unlocalized lesion	..	..	..	..	10	105	56	171
Hysteria; psychoneuroses, etc.	..	..	..	..	..	47	19	66
No evidence of intracranial lesion	..	..	..	..	..	67	20	87
Total								796

other cerebral hemisphere (changes in reflexes, loss of power, etc.) olfactory tests indicated the following localization:

Olfactory Interpretation	*Clinical Indication*
Lesion in right frontal or temporal lobe 5	Lesion in right cerebral hemisphere.. 5
	Lesion in left cerebral hemisphere.. 0
	Lesion in left cerebral hemisphere.. 4
Lesion in left frontal or temporal lobe 6	Lesion in right cerebral hemisphere.. 2
	Lesion in right cerebral hemisphere.. 5
Lesion in right cerebral hemisphere.. 5	Lesion in left cerebral hemisphere.. 0
	Lesion in left cerebral hemisphere.. 5
Lesion in left cerebral hemisphere.. 6	Lesion in right cerebral hemisphere.. 1

Therefore, in 19 of 22 patients (86 per cent) the localization by olfactory tests agreed with the clinical localization.

Localization of Supratentorial Tumors of the Brain by Olfactory Tests.—In 193 patients with verified supratentorial tumors of the brain, studies on minimal identifiable odor and on olfactory fatigue were made. The growths, found at operation or autopsy or by encepha-

lographic or ventriculographic examination, were in the following situations: frontal, temporal, frontotemporal or frontoparietal, 140 patients; parietal, parieto-occipital or occipital, 53 patients.

The results of the olfactory tests are summarized in table 7.

These figures demonstrate that more or less accurate localization of supratentorial tumors was possible in 62 per cent of all patients and that the percentage of localization was highest (74) in cases of growths in or around the frontal and temporal lobes. Localization as to both lobe and side was possible in 33 per cent, and here, again, the percentage was highest (37) in cases of growths in or around the frontal and temporal lobes. In some cases it was possible to conclude that the tumor was frontal rather than temporal, while in many instances one could not be certain whether the growth was in or under the frontal lobe or

TABLE 7.—*Results of Olfactory Tests on One Hundred and Ninety-Three Patients with Supratentorial Tumors of the Brain* *

Localization	Frontal and Temporal		Parietal and Occipital		All Tumors	
	Number	Percentage	Number	Percentage	Number	Percentage
Correct as to lobe	32	23	2	3.8	34	18
Correct as to side	19	14	3	4	22	11
Correct as to both lobe and side	52	37	12	23	64	33
		74		31		62
Not localized but olfactory function found disturbed	20	14	8	15	28	15
Localization in doubt	3	2	6	11	9	4.6
Incorrectly localized	3	2	4	7.5	7	3.6
Normal olfactory function	11	8	18	34	29	15

* See also table 3.

whether it was in the neighboring temporal lobe and was causing pressure on the frontal lobe.

Results of Olfactory Tests on Patients with Pituitary Tumor.—Of the 54 patients with pituitary tumors, 19 did not show clinical signs of pressure on the chiasm or optic nerves (defects in the fields of vision). In these patients, the growth was probably still confined beneath the dural diaphragm of the sella turcica, so that the extracerebral olfactory pathways (olfactory nerves, bulbs or tracts or olfactory roots) had not been pressed on. If these 19 patients are excluded, there remain the cases of 35 for analysis.

In 25 of the 35 patients (71 per cent) the values for the minimal identifiable odor were elevated, and in most of them they were high (between 15 and 30 cc. in each nasal passage). In 4 of the 25 patients there was also prolongation of olfactory fatigue (involvement of intracerebral olfactory pathways). For 1 of these 4 subjects the clinical diagnosis was pituitary adenoma and chronic encephalitis, and for

another, pituitary tumor and syphilis; the remaining 2 patients had received prolonged roentgen treatment before the tests were made.

Therefore, unilateral or bilateral elevation of values for the minimal identifiable odor without any prolongation of olfactory fatigue occurred in 40 per cent of all the patients with pituitary tumor in our series and in 68 per cent of all patients in whom there were signs of neighborhood pressure (field defects).

Results of Olfactory Tests on Patients with Infratentorial Tumor.—The quantitative olfactory tests have no value for the localization of tumors or other lesions in the posterior cranial fossa, nor are the tests of any value in distinguishing between supratentorial and infratentorial lesions.

Results of Olfactory Tests on Patients with Convulsive Seizures Not Due to Tumor.—Complete olfactory tests were made on 115 patients who

TABLE 8.—*Comparison of Results of Olfactory and Encephalographic Examinations in Patients with Convulsions Not Due to Tumor*

	Olfactory		Encephalographic	
	Number	Percentage	Number	Percentage
Normal	58	50	72	63
Diffuse changes	28	24	10	9
Localized lesion	19	17	26	23
Anosmia	8			
?	2	1.7	7	6
	115		115	
No localization	88	76	89	77

suffered from convulsive seizures not due to tumor or other demonstrable lesion. The clinical diagnosis was idiopathic grand mal. In all of the patients air was injected by the lumbar route either before or after the olfactory tests had been made, and in 36 mild or more pronounced cerebral atrophy or hypoplasia of one or both cerebral hemispheres was observed by the roentgenologist.

In table 8 the results of the olfactory tests are compared with those of the encephalographic examination.

COMMENT

The quantitative olfactory tests are subjective. The results depend on the proper cooperation of the patient and the correct interpretation of the time when he or she can first identify the odor of the substance introduced into the nasal passages. This is an inherent weakness of a test procedure which is not objective. However, the results appear to show that in a considerable number of patients the quantitative olfactory tests gave evidence of the location of the lesion.

In cases of subfrontal tumors of small size, the value for the minimal identifiable odor on one or both sides may be elevated without any prolongation of olfactory fatigue, but in cases of larger tumors which compress one or both frontal lobes, fatigue may also be prolonged beyond the normal period ipsilaterally or bilaterally. As is often the case, a lesion in or around one temporal lobe may involve the ipsilateral frontal lobe by pressure or may compress the ipsilateral extracerebral olfactory pathway. Under such conditions it will be impossible to infer whether the lesion is entirely frontal or whether the frontal signs are due to pressure from the lesion in the temporal lobe. In many cases, therefore, the olfactory tests cannot be used to distinguish between a lesion of and one adjacent to the frontal lobe.

It would be too much to expect that the functions of the olfactory pathways are disturbed in all or in most cases of intracranial lesions, any more than that an alteration of the visual fields or sensory or motor disturbances occur with all intracranial lesions. All that may be expected from the tests is that those who have an intracranial lesion so placed as to interfere with the functions of the olfactory pathways would show deviation from the normal in the results of quantitative olfactory tests. Therefore, it is not surprising that the largest number of positive results from the tests were found in patients with lesions in or around the frontal or temporal lobe of the brain.

When the lesion—tumor or other disease—was situated in or around the parietal or the occipital lobe, interference with the functions of the olfactory pathways occurred in only one third of the patients. Apparently, even in such cases the positive results with regard to disturbance of the sense of smell by the tests occurred more often with tumors in those situations and may have been due to distant pressure effects on the olfactory pathways.

SUMMARY

An analysis is made of the results of quantitative olfactory tests by the blast injection and stream injection of odorous substances in 1,000 patients admitted to a neurologic hospital.

Localization of intracranial lesions by the olfactory tests must be based on the combined results of tests for the value of the minimal identifiable odor and for the duration of olfactory fatigue.

The olfactory functions were found undisturbed in 341 patients (34.1 per cent).

Unilateral or bilateral elevation of the value for the minimal identifiable odor alone occurred in from 38 to 45 per cent of the patients with lesions in or around the frontal or temporal lobes. When patients with

diffuse disease and those for whom a clinical diagnosis had not been arrived at were excluded, unilateral elevation of the value for the minimal identifiable odor occurred in from 71 to 78 per cent.

On the basis of studies of fatigue alone, the lesions were correctly localized in 54 per cent and incorrectly localized in 18 per cent of the patients.

The quantitative olfactory tests were not found to have any value for the localization of tumors or other lesions in the posterior cranial fossa.

In 103 of 251 patients (41 per cent) with verified localized intracranial lesions of various kinds the olfactory tests were interpreted as correctly localizing the lesion, and in 33 (13 per cent), as giving incorrect localization.

In 120 of 193 patients (62 per cent) with supratentorial tumor it was possible correctly to localize the site of the lesion; localization was possible in 74 per cent of patients with tumors in or around the frontal or temporal lobe and in 32 per cent of patients with tumors in or around the parietal or occipital lobe of the brain.

In 91 per cent of the patients with complete anosmia there was a tumor in or around the frontal or temporal lobe of the brain.

Unilateral or bilateral elevation of the value for the minimal identifiable odor without any prolongation of fatigue was found in 40 per cent of patients with pituitary tumors and in 68 per cent of patients who had neighborhood pressure signs (defects in the fields of vision).

The results of olfactory tests on 115 patients with idiopathic grand mal are compared with the encephalographic observations on the same patients.

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LISSENCEPHALY

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Nature's embryologic mistakes allow an opportunity to study the development of the nervous system. When, for some unknown reason, the human brain stops its evolution at a stage in embryonic life, it becomes possible to see certain primordial characteristics of the brain structure. A state in the development of the human brain at which arrest is rarely seen is represented by lissencephaly,[1] or agyria. It is the usual condition of the adult brain of reptiles and lower animals but is not seen in the primates, of which even the lowest representatives have some evidence of fissuration of the cerebral cortex.

The following case of this anomaly in a child is reported.

HISTORY OF A CASE

History.—N. E. was delivered by low forceps and episiotomy of a primipara after a forty week gestation. Her weight at birth was 3,565 Gm. She breathed spontaneously. The maternal and paternal histories were not significant.

At the time of birth it was noted that the left eye was more prominent than the right and that the right upper eyelid drooped over the enophthalmic bulb. The movements of the eyes were not conjugate. The tension of the left eye was full, but that of the right eye could not be determined. The right pupillary margin was ragged, and vessels extended from the iris centrally to form a persistent pupillary membrane. On the left side a less prominent membrane was present. The right pupil was round, measured 6 mm. in diameter and did not react to direct light. The left pupil measured 3.5 mm. and was fixed. A yellowish red reflex was obtained on the left side, but on the right it was gray black with oblique illumination. It was possible to distinguish a grayish, irregular membranous material which lay deep behind the iris in the right bulb. The left eye could be transilluminated in all quadrants. At the 6 o'clock position a small, irregular, grayish nubbin was present posterior to the lens.

The patient was transferred to Bobs Roberts Hospital (service of Dr. D. N. Buchanan) on November 28, one week after birth. A fluctuant cephalohematoma, the size of a large hen's egg, was present in the left occipitoparietal region. No abnormalities were noted in the heart, lungs, abdomen or extremities. The fontanel was punctured, and at a depth of 1.5 cm. blood-tinged fluid was encountered. A lumbar puncture yielded similar blood-tinged fluid. Two days later another puncture of the fontanel was made and yellow fluid containing numerous red blood cells was obtained. Another puncture was made on December 4, and again yellow fluid

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From the Division of Neurological Surgery of the University of Chicago.

1. Owen (On the Anatomy of Vertebrates, London, Longmans, Green & Co., 1868, vol. 3) is said to have introduced the term lissencephaly (from the Greek, meaning "smooth brain") to describe the unconvoluted cerebral hemisphere.

was encountered. On December 11 the fontanel was punctured again and 30 cc. of clear, colorless fluid removed. On December 17, 40 cc. of fluid was removed and 1 cc. of phenolsulfonphthalein was injected. The dye was recovered from the opposite side immediately but could not be obtained from the lumbar subarachnoid space.

Repeated urinalyses revealed no abnormality. Examination of the blood showed normal white and red cell counts, a normal hemoglobin content and a normal distribution of leukocytes.

Roentgenograms of the skull showed that the fontanels were large.

A diagnosis of glioma of the retina with extension to the brain was made, and the patient was given roentgen therapy, receiving a total of 2,400 r in two series. Her condition did not change appreciably. While receiving the second course of roentgen treatments she suddenly died, at 5:10 p. m. on March 25.

A complete autopsy was performed by Dr. Paul E. Steiner. The significant observations were congenital malformations of the eyes and central nervous system, right microphthalmos, congenital malformations of the retina, intrauterine secondary glaucoma on the left side, hydrophthalmos, congenital cataracts, bilateral posterior synechia, bilateral bronchopneumonia, capillary hemangioendothelioma on the skin of the buttocks and lissencephaly.

Examination of the Eyes.—Right Eye: The right eye weighed 3.4 Gm. and measured 18 mm. anteroposteriorly and 19 mm. transversely. The cornea was 10 mm. in diameter, and the pupil, which was irregular, averaged 6 mm. in diameter. The wall was 15 mm. thick. Passing from the center of the optic disk to the center of the posterior surface of the large, partly opaque and slightly nodular lens was a thin white strand of tissue, less than 1 mm. in diameter. A white mass, 2 to 2.5 mm. in diameter and elevated 1.5 to 2 mm., lay on the optic disk.

Serial sections of the eye made possible a more precise study of the pathologic process. The anterior chamber was of normal size, at no point measuring more than 1.25 mm. in depth. The lens was 6 by 3 mm. in the maximal diameters. The ciliary process and iris were well developed. A pupillary membrane was adherent to the anterior surface of the lens capsule, and in places isolated fragments were seen attached to the capsule in the pupillary area. There was marked degeneration of the cortical lens fibers. Attached to the posterior lens capsule was a thin layer of retinal tissue, which at the periphery of the lens became thicker and was infiltrated with lymphocytes and occasional polymorphonuclear leukocytes. This layer of retinal tissue was detached from the choroid for a distance of 1 to 2 mm. posterior to the ciliary body. It then joined the atrophic, gliosed retina, which had none of its normal architectural characteristics and was densely pigmented (fig. 1*B*). Adjacent to the optic disk and filling in a coloboma was a mass of retinal tissue in which many rosette formations were present (fig. 2*B*). Extending from this mass of tissue was a strand of glial tissue surrounding the hyaloid artery, which passed to the posterior surface of the lens. Lymphocytes and very occasional polymorphonuclear leukocytes were present along the glial strand covering the persistent hyaloid artery. Clinging to its surface were pigment-laden macrophages.

The diagnosis was microphthalmia, coloboma of the optic disk, persistent hyaloid artery, congenital cataract and uveitis with posterior synechia.

Left Eye: The left eye weighed 8.1 Gm. and measured 24 mm. anteroposteriorly and 26 mm. transversely. The cornea measured 13 mm. and the pupil, which was circular, 12 mm. in diameter. The wall of the eye was thin, measuring 0.25 to 0.33 in thickness. The anterior chamber was shallow, being nowhere more than 2.5 mm. in depth.

Serial sections of the eye revealed thinning of the corneal epithelium. A few mononuclear cells, occasionally clumped, were present on the posterior surface of the cornea and on the anterior surface of the lens. There was degeneration

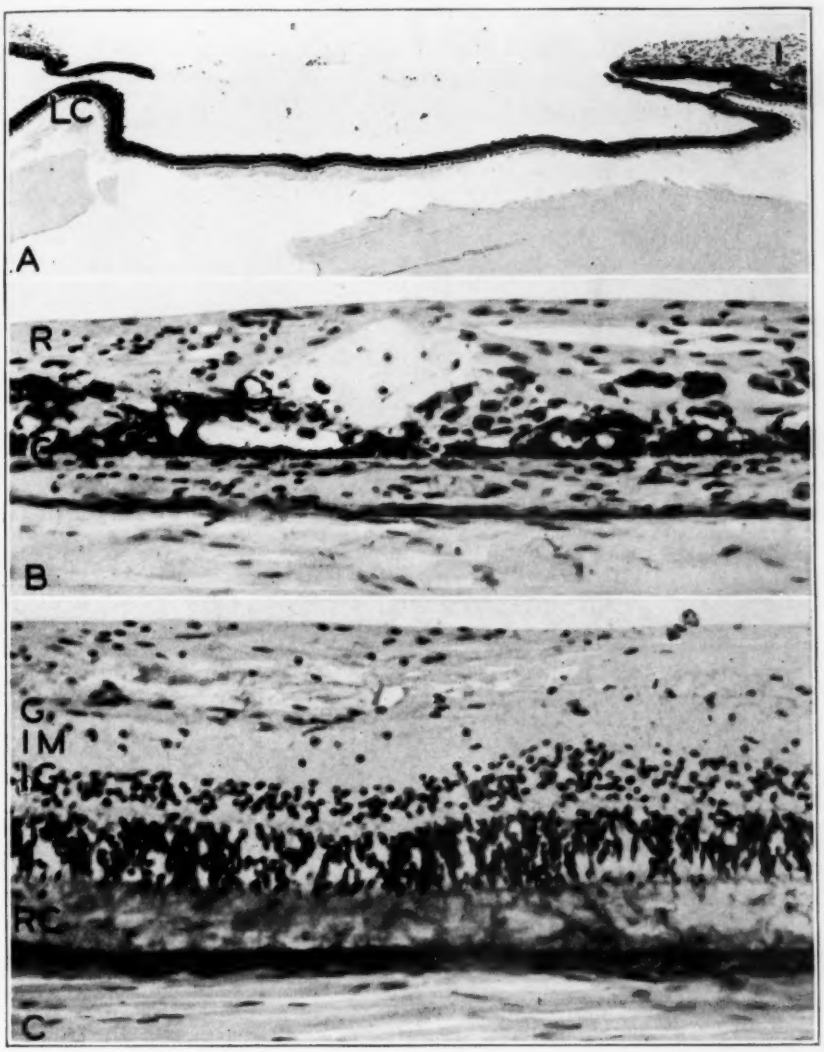

Fig. 1.—*A*, anterior surface of the lens of the left eye, showing the posterior synechia and iris pigment covering the lens capsule. *L. C.* indicates the lens capsule, and *I*, the iris. × 60.

B, retina of the right eye, showing gliosis and pigmentation. *R* indicates the retina, and *C*, the choroid. × 250.

C, retina of the left eye. *G* indicates the ganglion cell layer; *I M*, the inner molecular layer; *I G*, the inner granular layer, and *R C*, the layer of rods and cones, nuclei of which are in the suprajacent layer. × 250.

All the sections were stained with hematoxylin and eosin.

of the posterior lens fibers. The canal of Schlemm was patent. There was an annular marginal posterior synechia, and in places iris pigment covered the pupillary region of the lens capsule (fig. 1 *A*). Lymphocytes, plasma cells and pigment-laden macrophages sparsely infiltrated the iris and ciliary body, which were both atrophic. The retina was thin, containing few ganglion cells and showing gliosis of

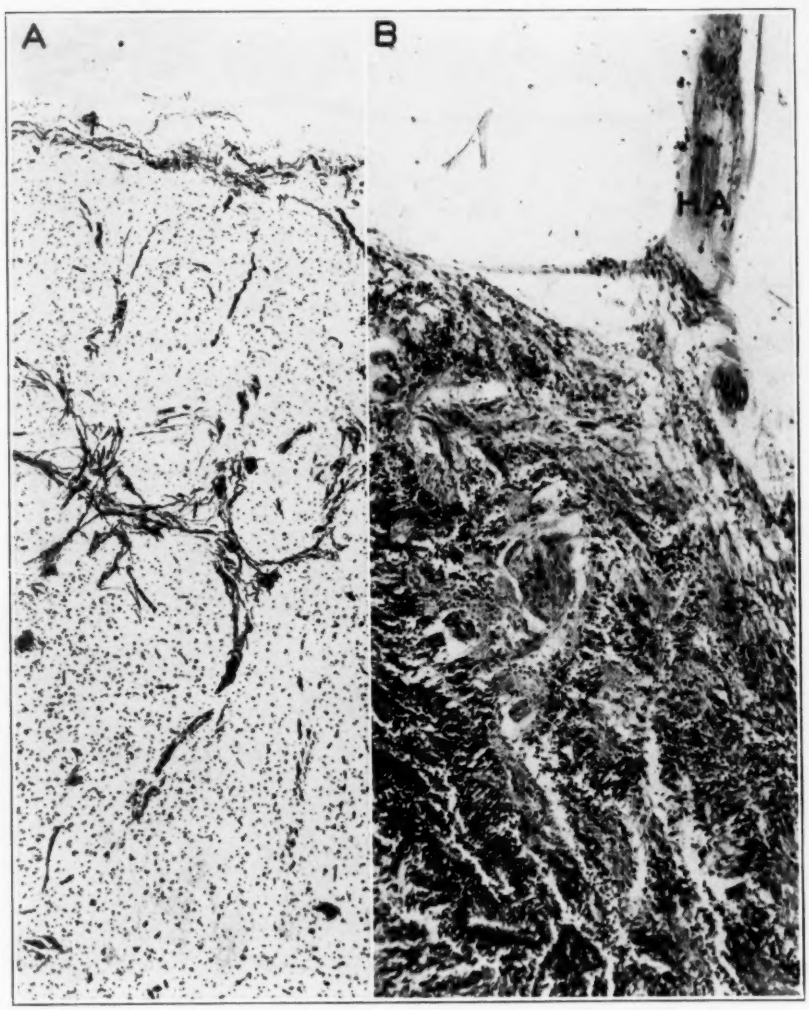

Fig. 2.—*A,* cerebral cortex impregnated to show reticulin, which is abundant. Perdrau preparation; × 55.

B, right optic nerve head, showing the persistent hyaloid artery (*HA*), and the rosette formation (at the left) in the undifferentiated retinal tissue filling in the coloboma. Hematoxylin and eosin; × 63.

the nerve fiber layer (fig. 1 *C*). Occasional lymphocytes and mononuclear cells were present on the retinal surface.

The diagnosis was buphthalmos, congenital cataract, endophthalmitis and posterior synechia.

Examination of the Brain.—The brain measured 17 cm. in length and 13 cm. in width. The superior surface of the cerebral hemispheres anteriorly was smooth and glistening, but laterally and posteriorly it was verrucous (fig. 3). The rostral

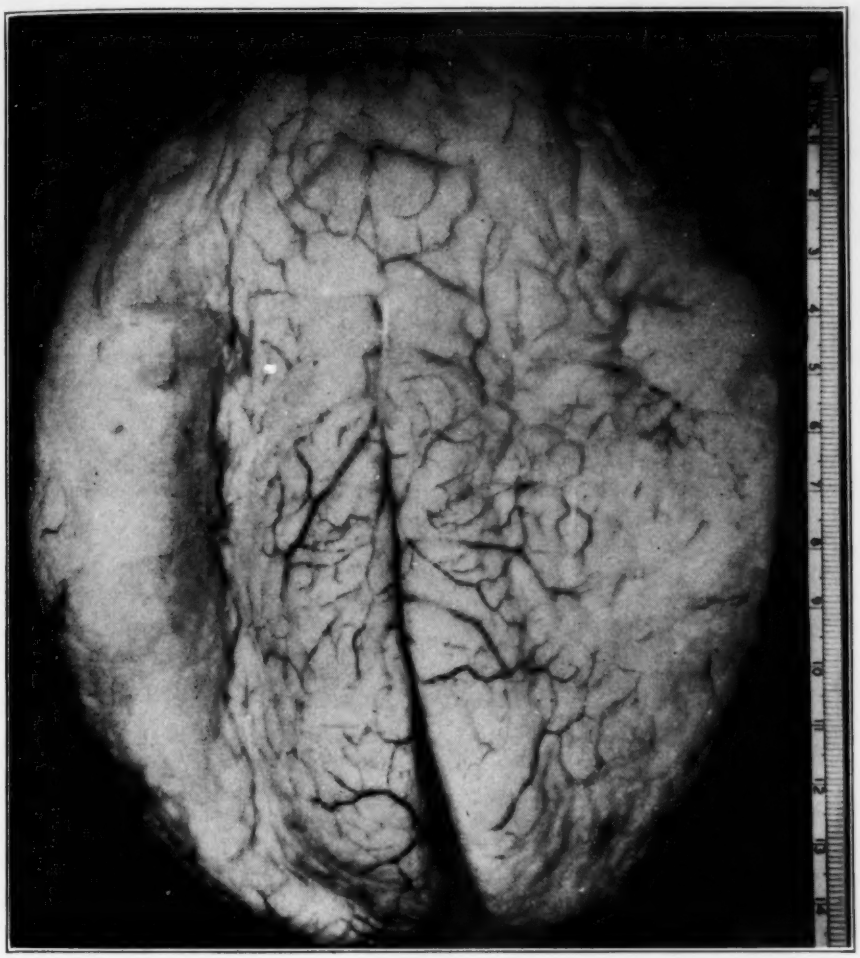

Fig. 3.—Superior surface of the cerebral hemispheres, showing lissencephaly and absence of the corpus callosum.

poles of the two hemispheres were joined, without a sagittal sulcus, as far posteriorly as 7.5 cm. from the frontal tip. At this point a shallow fissure, which deepened posteriorly, appeared in the midline and separated the two hemispheres. In this fissure was a thin, fenestrated membrane, representing the falx cerebri. The convexity of the hemisphere showed fine venous markings but no evidence of fissuration. On the inferior surface of the hemisphere the temporal lobe was

demarcated from the orbital surface of the frontal lobe by a fissure, which passed onto the lateral surface of the hemisphere as a shallow, broad groove (fig. 4 *A*). The orbital surface of the frontal lobe had been macerated in removal, but there appeared to be on each side a shallow groove passing laterally from the tip of the temporal lobe. The surface of both temporal lobes was smooth and glistening. The olfactory tracts were not evident. Both optic nerves could be identified passing out from the tissue paper–thin lamina terminalis. Between the two optic nerves was a slender optic chiasm, just behind which the pituitary stalk was visible. Posterior to it was the thinned-out floor of the third ventricle. The third cranial nerve on the left side appeared to be well developed; that on the right side was not visualized. The fourth nerve appeared to be present on both sides. The fifth, sixth, seventh, eighth, ninth and tenth cranial nerves were present on both sides. The cerebral peduncles were small. The circle of Willis appeared to be intact anatomically, even an anterior communicating artery being present.

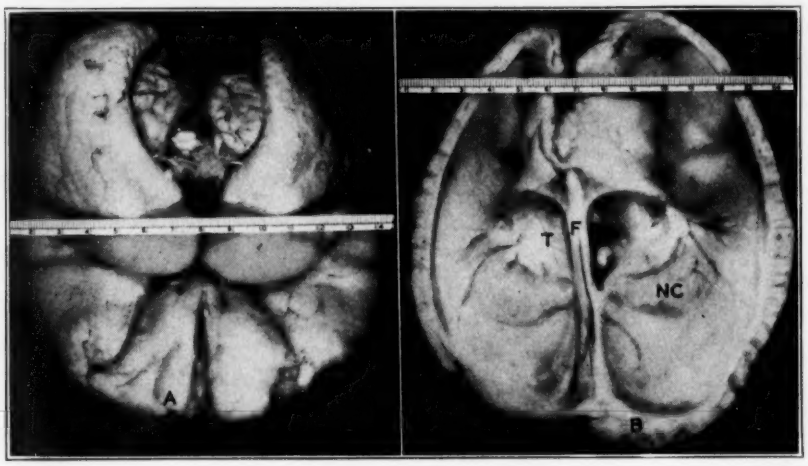

Fig. 4.—*A*, inferior view of the brain, showing the small agenetic cerebellum and the fissuration of the orbital surface of the frontal lobe.

B, floor of the cerebral ventricles, showing the enormous hydrocephalus, the fornix (*F*), the caudate nucleus (*NC*) and the thalamus (*T*).

The cerebellum was small, measuring 4.5 cm. in width and 3.0 cm. in height. The posterior portion of the vermis was absent. The two hemispheres were connected by a nodule passing across the anterior portion of the cerebellum. The fourth ventricle was notably dilated, measuring 1.5 cm. in all diameters. A horizontal section through the cerebral hemispheres revealed massive dilatation of the ventricular system, which communicated across the midline both by way of the foramens of Monro and through another opening in the midline above the fornices (fig. 4 *B*). The latter were composed of two strands of white matter, 3 cm. long. The lateral ventricles measured 12 cm. in width and 13.5 cm. in length. The third ventricle was 2 cm. in width and 4.5 cm. in length. Projecting into the anterior part of each lateral ventricle was a round, gray eminence, measuring 4.3 cm. in length and 1.6 cm. in width, which represented the striate body. Between this protuberance and a small elevation representing the thalamus

was a shallow groove. The walls of the cerebral ventricles were smooth and glistening except for several nodules measuring 2 to 3 mm. in diameter and elevated about 1 mm. above the floor of the inferior horn. The choroid plexus lay along the lateral margin of a sheath of tissue (tela choroidea) which passed laterally from the fornix across the thalamus. This rectangular sheath of tissue formed the roof of a large cavity (dilated suprapineal recess) which extended posteriorly above the corpora quadrigemina and appeared to communicate with a thin-walled arachnoid cyst lying over the cerebellum. Through the middle of this space passed the vein of Galen, which posteriorly terminated in a thin strand of tissue attached to the right occipital pole. The floor of this cavity was formed by the thalami and tegmentum mesencephali. Transversing it caudally was the posterior commissure. A small dimple just anterior to this commissure represented the oral part of the aqueduct of Sylvius, which appeared to be occluded about 5 mm. from its beginning.

The corpora quadrigemina were remarkably well developed but poorly differentiated into superior and inferior bodies. The massa intermedia was represented by a thin strand of tissue 1.5 cm. in length and 1 or 2 mm. in thickness.

Blocks containing the basal ganglia, thalami, mesencephalon, pons, medulla and cerebellum were taken for serial sectioning, every twenty-fifth section being stained by the Nissl method and the adjacent section by the Smith-Quigley technic for myelin. Representative blocks were taken from various parts of the cerebral cortex, and sections made from them were stained by Nissl's technic for myelin and impregnated by Globus' modification of Cajal's gold chloride-mercury bichloride method for astrocytes, Penfield's method for oligodendroglia and microglia, Bodian's method for nerve fibers, Perdrau's technic for reticulin and Bielschowsky's method for nerve cells.

Cerebral Cortex: Sections from various areas of the cerebral cortex showed no evidence of the normal cytoarchitectural or myeloarchitectural appearance. The tissue which corresponded to the cortex was made up of masses of irregularly arranged cells, at times clumped together with a tendency to radial distribution and at others without any suggestion of an orderly arrangement (fig. 5). In places the cortex contained numerous cells and in others very few cells. The outer layer, the *Randschleier,* could scarcely be recognized in most parts of the cortex so densely was it packed with nerve cells and glia. Beneath this numerous neurons could be seen. The individual nerve cells had a small amount of faintly staining cytoplasm and occasionally contained vacuoles. The nucleus stained darkly, and the nucleolus could be made out only with difficulty. The processes of the cell body stained rather intensely and were corkscrew shaped in most instances. There was a pronounced increase in astrocytes, which did not appear abnormal. The oligodendrocytes seemed to be decreased in number and in the white matter did not lie in parallel rows. There was a definite increase in the number of blood vessels in the cerebral cortex. Microglia cells were seen scattered throughout, in many places having a rodlike appearance. Here and there were nodules consisting of a few neurons and many glia cells. The pia-arachnoid was poorly developed, and there did not appear to be a space corresponding to the subarachnoid space, although a few blood vessels were seen to run in the pia-arachnoid. Perdrau sections demonstrated the definite increase in blood vessels in the cortical areas. Here and there marked proliferation of reticulin extended from the blood vessel into the adjacent nerve tissue (fig. 2 *A*). The blood vessels otherwise appeared normal. The ependymal surface of the ventricle was in most places lined by thinned-out ependymal cells, with several deeper layers of bipolar spongioblasts

arranged parallel to the surface of the ventricle. About the nerve cells was frequently seen a halo, indicative of edema of the cortex. Only an occasional myelinated fiber was seen beneath the cortex in myelin-stained sections.

Fig. 5.—Cerebral cortex, showing the poorly differentiated outer zone (*R*), a germinal center (*G*), the *Markschicht* (*M*) and ependymal layers (*E*).

Bielschowsky and Bodian preparations of the cerebral cortex showed a considerable number of unmyelinated nerve fibers, slightly beaded, passing radially from the cortex into the subcortical white matter. The neuronal structures did not impregnate well. They were usually shrunken and angular, and the cytoplasm

not infrequently contained one or more vacuoles. Many of the nerve cells had corkscrew processes. The nerve fibers from the cortex in general seemed to pass radially. At times the nerve fibers were matted together or passed parallel to the surface of the cortex, usually in bunches of six or seven.

Penfield's technic impregnated certain of the microglia cells with discontinuous processes. Oligodendrocytes were rarely seen. The pronounced increase in astrocytes was well seen in gold chloride–mercury bichloride preparations, particularly in the white matter and to a lesser extent in the gray matter. The astrocytes did not seem to extend into the subependymal layer. Most of the astrocytes were rather large and fibrous.

Perdrau preparations showed that the arachnoid had relatively little reticulum and was firmly attached to the cortex and brain stem.

Basal Ganglia: The changes in the neurons were common to all parts of the nervous system and will not be described for each nucleus. The cell shrinkage, the diffusely staining nucleus and nucleolus, the vacuolated cytoplasm and the corkscrew processes could be seen in varying degrees in all of the nuclei.

The basal ganglia appeared to be well developed. The caudate nucleus and putamen were of considerable size. The claustrum was disorganized but could be recognized. The capsula externa and capsula extrema were present. The globus pallidus was likewise normally developed; both the inner and the outer portion were present. Myelination was poor, but the laminas could be recognized. The subthalamic body was of normal size and contained the normal complement of neurons. The substantia nigra was present and had approximately a normal number of cells. The neurons, however, did not contain pigment.

Thalamus and Hypothalamus: Both these ganglia were greatly distorted by the extreme hydrocephalus. The hypothalamus could be recognized and certain nuclei identified. The supraoptic nucleus was readily seen and appeared relatively normal. The paraventricular nucleus was present. Other nuclear masses were present but, because of their less distinct cytoarchitectural and topographic features, could not be identified with certainty. The mamillary bodies could be recognized and appeared fairly normal.

Many of the thalamic nuclei were present. The anterior group, however, could not be demonstrated with certainty. The medial nucleus (nucleus medialis dorsalis) was present, although small and distorted. The lateral nuclear mass was easily recognized, although the neurons were unusually sparse, and considerable gliosis was evident, particularly in the nucleus ventralis lateralis. The nucleus ventralis posterior was present and contained many cells. The centrum medianum was present but small. The intralaminar nuclei could not be recognized with certainty. The pulvinar was present and contained neurons, but many glial islands were seen, particularly in the lateral portion of the pulvinar. The nucleus lateralis dorsalis was well formed. The lateral and medial geniculate bodies could not be seen. The optic tract broke up into a number of fascicles, which terminated in masses of glia along the mesencephalotemporal sulcus. There was no evidence of lamination. The medial geniculate body was not present; not even a glial mass could be seen as its representative.

Mesencephalon: The structures of the mesencephalon, the inferior and superior colliculi and the tegmentum, could be identified. The tegmentum was small. The brachium conjunctivum could be recognized and followed from the cerebellum, but it contained few fibers. The red nucleus was compact and had many neurons. The nuclei of the third cranial nerve were well developed, and the neurons appeared fairly normal. The fibers of the pes pedunculi were few. The fibers of the

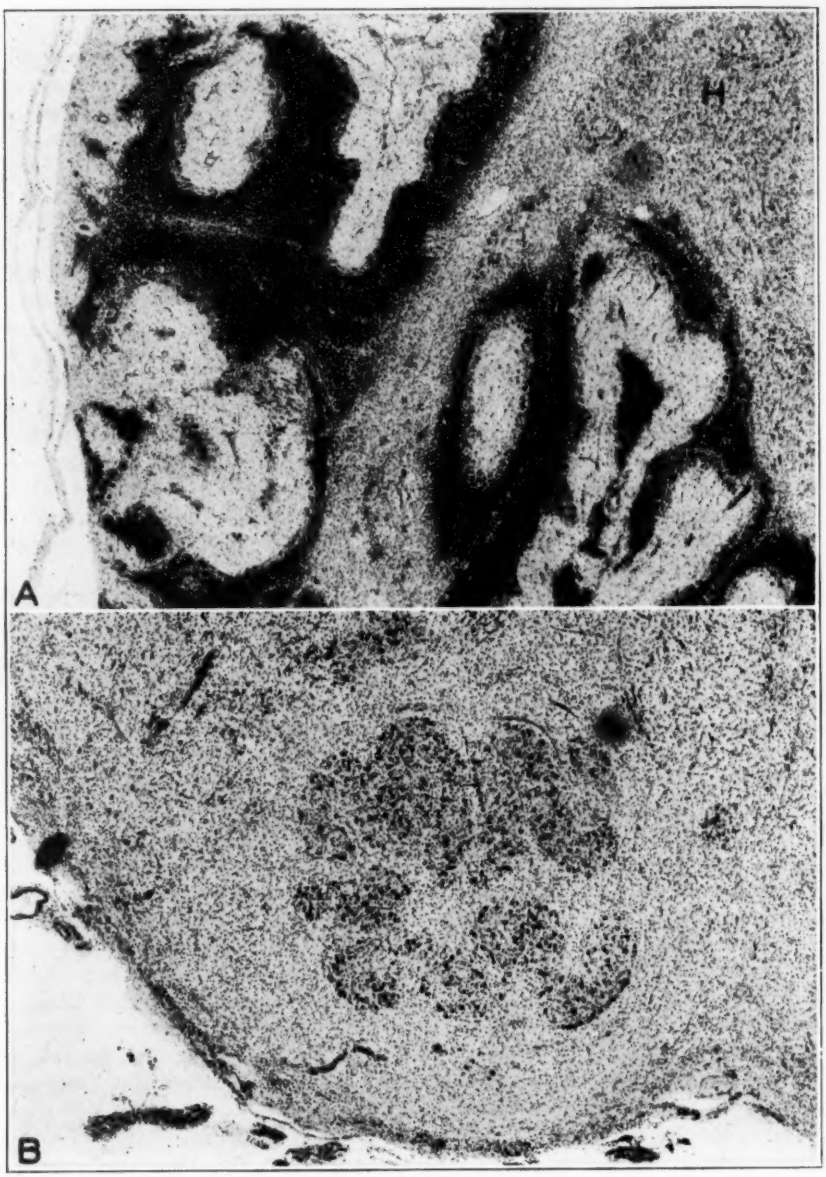

Fig. 6.—*A*, a cerebellar folium, showing the simple pattern, the variation in thickness of the granular layer and a heterotopia (*H*) in the white matter, composed of cells resembling those of the dentate nucleus. Nissl stain; × 30.

B, olivary region, showing the absence of the pyramidal tracts and the poorly developed inferior olivary nucleus. Nissl stain; × 25.

ascending sensory tracts were not myelinated and could not be definitely recognized. The aqueduct of Sylvius was patent; in several places it was very narrow, a condition which was all the more striking in comparison with the remainder of the ventricular system.

Pons and Medulla: The cerebellar peduncles were small and poorly developed but could be recognized. Outstanding was the fact that the pontile nuclei were well developed, numerous and practically normal. The longitudinal fibers passing through the pons were few. The cells of the nuclei of the motor fifth, sixth and seventh cranial nerves were normal in both qualitative and quantitative appearance. The cells of the main sensory root of the trigeminal nerve were numerous but stained rather palely. The cells of the cranial nerve nuclei of the medulla were likewise well preserved and numerous. The nuclei of the posterior column were well developed. The arcuate fibers from the nuclei of the posterior column were poorly myelinated or unmyelinated. Accordingly, the stratum interolivare was poorly myelinated. The descending root of the fifth cranial nerve was well developed, and its nucleus was prominent. The pyramids were practically absent. The inferior olivary nucleus was crudely developed (fig. 6*B*). It was roughly circular, but the cells, instead of forming regular curves, were clumped, giving rise to an irregularly convoluted mass. The fleece was fairly well developed. The accessory olivary nuclei were present.

Although the general contour of the brain stem was preserved, there was a mass of glia about its entire periphery with the exception of the ventricular surfaces. This mass of glia fused with a thickened arachnoid. There was hence no subarachnoid space.

Cerebellum: The cerebellum was notably anomalous. The fissuration could not be identified. Most of the fissures were shallow, and the folial pattern was simple. The cerebellar cortex and folia were scattered rather irregularly over the cerebellar white matter, with occasional areas that were not covered with cortex. The structure of the cerebellar cortex was abnormal. The molecular layer was thick but not separated from the arachnoid. There was no evidence of Obersteiner's cellular layer. The Purkinje cells were poorly developed but present in abundance. The molecular layer was thin and sparsely cellular. In some sections the dentate nucleus was readily recognizable, although it was rarely complete, a portion of the horseshoe being absent. In many sections, however, clumps or masses of cells (heterotopias) were scattered throughout the cerebellar white matter, which resembled the cells of the dentate nucleus. Occasional glial nests were encountered (fig. 6*A*).

COMMENT

A number of features, each a rarity, made this case unique. The absence of fissuration of the cerebral cortex, the agenesis of the corpus callosum, the lack of ocular development, the incomplete formation of the cerebellum and the maldevelopment of the subarachnoid space are unusual occurrences. Superficially considered, they represent an arrest in the development of the brain at approximately the third month of fetal life. It is at this time that the cerebral hemispheres are agyric, that the spinal fluid begins to form the subarachnoid channels and that the cerebellum is in the process of formation. But the multiple anomalies in this case cannot be entirely explained by an arrest of development at one or more stages in embryonic evolution. There was a superimposed

abnormal development of the tissue, so that the end result was a curious mixture of hypoplasia and dysplasia. In other words, after a temporary arrest certain cells became active again, but their further differentiation, perhaps as the result of the arrest, was abnormal. These processes will be discussed in relation to each of the anomalies.

Agenesis of the Corpus Callosum.—The anomaly of the corpus callosum in this case differed from the absence of the corpus callosum as demonstrated pneumoencephalographically; in the latter condition there is no nerve connection between the two hemispheres, whereas in the present case the two hemispheres were confluent. This condition apparently resulted from failure of the cerebral vesicles to develop separately. Since in the 5 week human embryo (His [2]) the two hemispheres are divided by a midline groove, the arrest of development must have occurred at about the fetal age of 4½ weeks. The presence of a sagittal sulcus separating the two hemispheres posteriorly is an example of the peculiar fact that developmental defects do not affect all parts of the brain equally.

Lack of Ocular Development.—The ocular anomalies in this case represent an arrest of development at approximately the fetal age of 3 months. At this time the fetal fissure is closing, the lens has separated from the surface and the primary lens fibers have formed (Mann [3]). Retinal differentiation is just beginning. In the present case the masses of neural tissue in the right eye were evidence of this undifferentiation of the retina. The right eye was, therefore, an example of microphthalmia with dysgenesis of the retina. In the left eye the retina was developed but atrophied and degenerated. This degeneration may have been secondary to the distention of the eyeball by vitreous fluid, as the result of adhesions between the iris and the lens. This intrauterine secondary glaucoma is a rare condition and is distinguished from true buphthalmos by the fact that the anterior chamber is not dilated but shallow.

The frequency of ocular pathologic changes in association with lissencephaly is difficult to determine, since the eyes were not examined at autopsy in the other reported cases. It is noteworthy that in at least 2 of the 5 reported cases the pupils did not respond to direct light. In none of the cases except de Lange's [4] was an ophthalmoscopic examination reported, and in this instance no abnormality was noted.

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2. His, W.: Développement de la substance grise de l'écorce cérébrale, Cong. internat. d. méd., Compt. rend., 1900, Sect. d'histol. et d'embryol., pp. 56-57; Die Entwicklung des menschlichen Gehirns während der ersten Monate, Leipzig, S. Hirzel, 1904.

3. Mann, I.: Developmental Anomalies of the Eye, London, Cambridge University Press, 1937.

4. de Lange, C.: Lissenzephalie beim Menschen, Monatschr. f. Psychiat. u. Neurol. **101**:350-381, 1939.

Cerebellar Aplasia.—It is well known that the posterior portion of the cerebellar vermis is the last to develop ontogenically. This has been advanced as an argument for the theory of congenital inclusions as the cause of cerebellar medulloblastoma. The lack of development of this part of the cerebellum in this case is readily understood. But the entire cerebellum was abnormal. The folial pattern was simple. The structure of the cerebellar cortex was anomalous; the Purkinje cells were poorly developed; the molecular layer was sparse; the dentate nucleus was of abnormal shape, and numerous heterotopias surrounded it. These abnormalities of the cerebellum appear to be a fairly constant feature of the lissencephalic brain, for they are mentioned in most of the reports in which the cerebellum is described. Perhaps in association with these cerebellar anomalies should be noted the crude primitive arrangement of the inferior olivary nucleus.

Agenesis of the Subarachnoid Space.—At approximately the fetal age of 10 weeks the subarachnoid space becomes a pathway for the cerebrospinal fluid. Ventricular fluid is present three to four weeks prior to this time, but it does not find its way out of the ventricular system until a month later. It is assumed that the ventricular fluid, by seeping into the coverings of the brain, forms the subarachnoid space. When the subarachnoid space fails to develop, the ventricular fluid does not have access to the absorbing mechanism and hence hydrocephalus develops. This is not a usual feature of lissencephaly, for it was present in none of the other cases. It seems likely that the spinal subarachnoid space in this case developed more or less completely, since a lumbar puncture yielded cerebrospinal fluid. Unfortunately, the spinal cord was not available for study.

Aplasia of the Cerebral Cortex.—The development of the human cerebral cortex has been described in detail by His [2] and Brunschweiler.[5] In the fetus of 1.5 to 2.5 cm. two layers can be distinguished in the cortical area, an outer fibrillar and an inner cellular layer. The inner zone consists of columns of cells arranged at right angles to the ventricular wall. This is the matrix from which the cortex will be evolved. The outer layer, almost devoid of cells, is the *Randschleier* of His. Between the two are a number of horizontal cells, irregularly placed, which represent the anlage of the stratum cribosum. Just outside the *Randschleier* is mesodermal tissue with hematopoietic elements, which will form the meninges.

At the end of the second month of fetal life a change occurs. A zone of sparse cells begins to form in the matrix beneath the internal

5. Brunschweiler, H.: Contribution à la connaissance de la "microcephalia vera," Schweiz. Arch. f. Neurol. u. Psychiat. **21**:246-282, 1927; **22**:73-121 and 269-309, 1928.

margin of the *Randschleier*. In this new zone (the intermediate zone) are piriform and fusiform cells arranging themselves in a radiating fashion. At the margin of this layer round granular cells appear. Thus at the end of three months four layers are present, the outer *Randschleier*, the anlage of the cortical layer, the clearer intermediate zone and the matrix.

Shortly afterward at the junction of the matrix and the intermediate zone a further modification occurs. The area, which has been densely filled with undifferentiated cells, begins to have somewhat elongated cells, which lie tangentially. This is the first evidence of the *Markschicht*, which will form the white matter.

At the 4 month stage the cortical zone, composed of granular cells in radiating columns, is thicker, and the part immediately beneath the *Randschleier* is extremely dense in cells. The boundary between the *Randschleier* and the cortical zone is sharp, but that between the cortical and the intermediate zone is less clear. The intermediate zone has also increased in depth and contains many differentiated cells, well oriented in a radial arrangement. The fourth layer, the *Markschicht* is distinct and contains many elongated, fusiform cells, multipolar cells and cells with round nuclei similar to those in the matrix. The cells are irregularly arranged in the *Markschicht*. The cells of the fifth layer are still undifferentiated, granular and occasionally clumped (*Keimzellen*).

At 6 months of age the different layers have still enlarged. The *Randschleier* still contains cells, but at the eighth month they have largely disappeared. The cortical layer is still dense but is beginning to show the divisions into the six layers of the normal cortex. The intermediate zone and the spongy parts of the matrix are enlarged, so that the *Markschicht* is beginning to be effaced, a condition which occurs about the eighth month.

At the eighth month the cortical layer has largely differentiated and shows somewhat the arrangement of the fully developed cerebral cortex. The matrix is reduced almost to the ependymal cells alone. The intermediate zone, the *Markschicht* and the spongy part of the matrix have formed the white matter.

It is evident that in the present case the arrest of development of the cortex did not cause complete aplasia at one stage. Certain characteristics seen in this cortex—the status verrucosus and the arrangement of the cortical layer—are typical of an early stage of evolution, while others—the development of the white matter and the absence of the matrix—are evidence of more complete maturation. Moreover, certain anomalies, such as the absence of the *Randschleier*, cannot be explained on a simple aplastic basis, since this zone is a feature of the cortex from almost the beginning of differentiation in the cerebral vesicles. The

anomalous development of the cerebral cortex in this case is, then, the result of a partial arrest of the normal evolution with abnormal differentiation of certain constituents of the cortex.

LISSENCEPHALY

Absence of cerebral fissuration, agyria or lissencephaly, is a rarity, although numerous reports of pachygyria or partial agyria have accumulated in the literature (Vogt,[6] Jacob,[7] Bielschowsky,[8] Grawitz[9] and others). It is therefore advisable to review the reported cases of lissencephaly, so that a clear conception of this condition may be gained.

Review of Reported Cases.—Two cases of lissencephaly were reported in 1914.

Culp's Case: Culp[10] described 1 case in his doctorate thesis at the University of Heidelberg. The brain which he studied was that of a 4 month old boy, born of the third pregnancy of normal parents. The child's head measured 39 cm. in circumference. The extremities were moved feebly and occasionally exhibited a muscular spasm. The pupils did not react to light. At 3 months of age the child had an epileptic attack. Shortly afterward he began to vomit, fever developed and he died of pneumonia.

A complete autopsy revealed no abnormalities other than those in the lungs and brain. The brain presented no fissuration other than the sylvian fissure. The insula was not developed. The corpus callosum was rudimentary (no further description was given). The septum pellucidum was absent, allowing the two slightly enlarged ventricles to communicate freely. The basal ganglia were grossly normal. The cerebellum was small, but otherwise appeared well developed. Histologic examination of the brain revealed lack of differentiation of the cerebral cortex, which showed status verrucosus simplex. Heterotopic collections of cells were seen in the white matter, and groups of Cajal fetal cells were seen near the basal ganglia.

Ehrhardt's Case: Ehrhardt[11] reported the second case to be recorded in 1914. The brain he described was that of a 9 year old female spastic idiot, who died of pulmonary tuberculosis. Her development had always been retarded.

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6. Vogt, H.: Ueber die Anatomie, das Wesen und die Entstehung mikrocephalen Missbildungen nebst Beiträgen über die Entwicklungsstörungen der Architektonik des Zentralnervensystem, Arb. a. d. hirnhaut. Inst. in Zürich **1**:1-203, 1905.

7. Jacob, H.: Genetisch verschiedene Gruppen entwicklungsgestörter Gehirne, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:615-648, 1938.

8. Bielschowsky, M.: Ueber die Oberflächengestaltung des Grosshirnmantels bei Pachygyrie, Microgyrie and bei normaler Entwicklung, J. f. Psychol. u. Neurol. **30**:29-76, 1923.

9. Grawitz: Ein Fall von Aplasie der Grosshirnhemisphären, Deutsche med. Wchnschr. **17**:146-147, 1891.

10. Culp, W.: Ein Fall von vollkommenem Mangel der Grosshirnwindungen, Inaug. Dissert., Heidelberg, Mainz, Mainzer Verlagsanstalt und Druckeri, 1914.

11. Ehrhardt, A.: Ueber Agyrie und Heterotopie in Grosshirn, Allg. Ztschr. f. Psychiat. **71**:656-670, 1914.

The brain weighed 800 Gm. and was smooth except for the sylvian fissure and shallow sulci in the frontal region. Ehrhardt noted that the gray matter covering the cerebral hemispheres was much thicker than normal, occupying more than one-half the thickness of the wall of the hemisphere. The cortex was differentiated into four layers. The basal ganglia and cerebellum appeared grossly normal.

Brunschweiler's Case: The next case in chronologic order was reported by Brunschweiler.[5] No clinical history was available.

The cerebral hemispheres were smooth except for the sylvian fissure and a callosomarginal sulcus. The corpus callosum was deficient posteriorly. The wall of the cerebral hemisphere was composed of poorly differentiated layers of gray matter. The cerebellar folia were simple and poorly developed. Heterotopias were presented in the frontal lobe, cerebellum and brain stem. The olivary nuclei were poorly developed. The thalamus was shrunken, and the nuclei were poorly differentiated.

Koch's Case: Koch [12] reported the case of an idiot boy aged 8½ months with diplegia and amaurosis. The pupils were unresponsive to direct light, and there was spontaneous horizontal nystagmus. The limbs were flaccid and paretic.

The brain weighed 820 Gm. The cerebral hemispheres were smooth except for the sylvian fissure, the inferior temporal sulcus and shallow orbital sulci. The optic nerves, brain stem and cerebellum appeared normal. The corpus callosum was well developed. The claustrum and insula were not developed. Histologic studies showed that the temporal cortex was differentiated into six layers, while in the frontal region but four layers were found.

Lange's Case: The most recently reported case of lissencephaly was described by de Lange,[4] that of a 10 month old boy who had generalized convulsions at the age of 5 months. The pupils reacted to direct light, and the fundi appeared normal. The patient was hypertonic in all four extremities. There was marked poverty of motion. The child died, without apparent cause.

The brain weighed 700 Gm. Its surface was smooth except for the sylvian fissure and the superior temporal, callosomarginal and orbital sulci. The cerebral cortex was thick and poorly differentiated. The claustrum was not present. The diencephalon and mesencephalon were relatively normal. There were heterotopias in the cerebellum and brain stem. The dentate nucleus was anomalous, having few convolutions. The olivary nuclei were broken up into several pieces, one large part of the nucleus being situated on the corpus restiforme.

Von Monakow's [13] Case: This case has been mentioned as an example of agyria but should not be so included, since the greater part of the wall of the cerebral hemisphere was merely a thick membrane, without any evidence of cortical tissue.

Clinical Features.—There does not appear to be a clinical picture pathognomonic of lissencephaly. Although spasticity was noted in most of the cases, less than half the patients were mentally retarded, and less than half had epileptic attacks. That the clinical findings were not more prominent and consistent is perhaps due to the fact that, with 1 exception,

12. Koch, W.: Ein Fall von nahezu totaler Agyrie des Grosshirns, Beitr. z. path. Anat. u. z. allg. Path. **97**:247-260, 1936.

13. von Monakow, C.: Biologisches und morphogenetisches über die Microcephalia vera, Schweiz. Arch. f. Neurol. u. Psychiat. **18**:3-39, 1926.

none of the patients lived to be more than 1 year of age. Ehrhardt's [11] patient reached the age of 9 years. Two of the 6 patients were considered blind; perhaps others were also, but, owing to their age, the condition could not be detected.

In spite of the fact that the cerebral cortex is not developed, patients with this anomaly are not completely paralyzed. Sufficient motor power is present so that, at least in some cases, the child's muscular system is not considered abnormal. This supports the clinically accepted theory that most of an infant's motor system is subcortically innervated.

Pathologic Features.—Aside from the characteristic which gives the condition its name, certain pathologic features seem to be present in lissencephaly. The development of the cerebral cortex in all cases is greatly retarded. In the majority of cases the development of the cortex is considered to be at a stage comparable to that of a 3 month fetus. The cortex is very thick, and the underlying white matter is thin. Cortical lamination, with the exception of the outer zone, or *Randschleier,* is poorly developed or absent. "Germinal centers," verrucous formations and heterotopias are frequently present.

In striking contrast to the cerebral cortex, the basal ganglia and brain stem are well developed. But the cerebellum and the olivary nuclei exhibit notable anomalies, usually of the nature of hypoplasia, although heterotopias are frequently seen in both regions. Hydrocephalus is not of usual occurrence and presumably is due to a coincident developmental anomaly of the arachnoid membrane.

SUMMARY

The case of a hydrocephalic child is reported in which the cerebral hemispheres were agyric, the corpus callosum absent, the subarachnoid space poorly developed, the cerebellum and cerebral cortex anomalous and both eyes maldeveloped. The multiple anomalies in this case are considered to be due to a curious mixture of hypoplasia and dysplasia. The lissencephalic state in the human being is discussed and its rarity emphasized by a review of the literature, in which only 5 cases are reported.

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THE ARNOLD-CHIARI MALFORMATION

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The Arnold-Chiari malformation is a deformity of the hindbrain in which there is displacement of parts of the cerebellum and brain stem through the foramen magnum into the upper part of the vertebral canal.

It was first observed by Arnold [1] in 1894 in a newborn infant with lumbosacral spina bifida and a large *Myelocyste*. A portion of the cerebellum extended downward through the foramen magnum as a tonguelike process overlying the dorsal aspect of the spinal cord as low as the midcervical level. The lower portion of the elongated fourth ventricle was contained within the vertebral canal, and the vermis of the cerebellum was poorly developed.

In an analysis of 63 cases of hydrocephalus, Chiari,[2] in 1895, described in great detail the deformities of the hindbrain and classified the changes under three types according to the degree of the displacement.

1. Elongation of the tonsils and medial parts of the inferior lobes of the cerebellum as a tonguelike process enveloping the medulla in the upper portion of the vertebral canal. The brain stem may be elongated, but the fourth ventricle is not carried down below the foramen magnum (fig. 1 *A*).

2. Displacement of parts of the cerebellum into the upper part of the vertebral canal, within which is also contained the lower portion of the elongated fourth ventricle. The whole brain stem is always elongated, and the foramens of the fourth ventricle open into the spinal subarachnoid space below the foramen magnum (fig. 1 *B*).

3. Herniation downward of the whole hydrocephalic cerebellum into a cervical spina bifida and meningocele (fig. 1 *C*).

In his collection Chiari had 14 cases of type 1, in 1 of which there was associated internal hydrocephalus with spina bifida and myelomeningocele and in 13 only internal hydrocephalus. The ages varied from 3½ months to 68 years, the majority of patients being adults. There were

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1. Arnold, J.: Myelocyste, Transposition von Gewebskeimen und Sympodie, Beitr. z. path. Anat. u. z. allg. Path. **16**:1, 1894.

2. Chiari, H.: Ueber Veränderungen des Kleinhirns, des Pons und der Medulla oblongata in Folge von congenitaler Hydrocephalie des Grosshirns, Denkschr. d. k. Akad. d. Wissensch. Math-naturw. Kl. **63**:71, 1895.

7 cases of type 2, in all of which there was internal hydrocephalus with spina bifida. An associated myelomeningocele was present in 5 cases, meningocele in 1 case and spinal rachischisis in 1 case. The ages in this group ranged from birth to 6 months. Only 1 case was of type 3, that of a

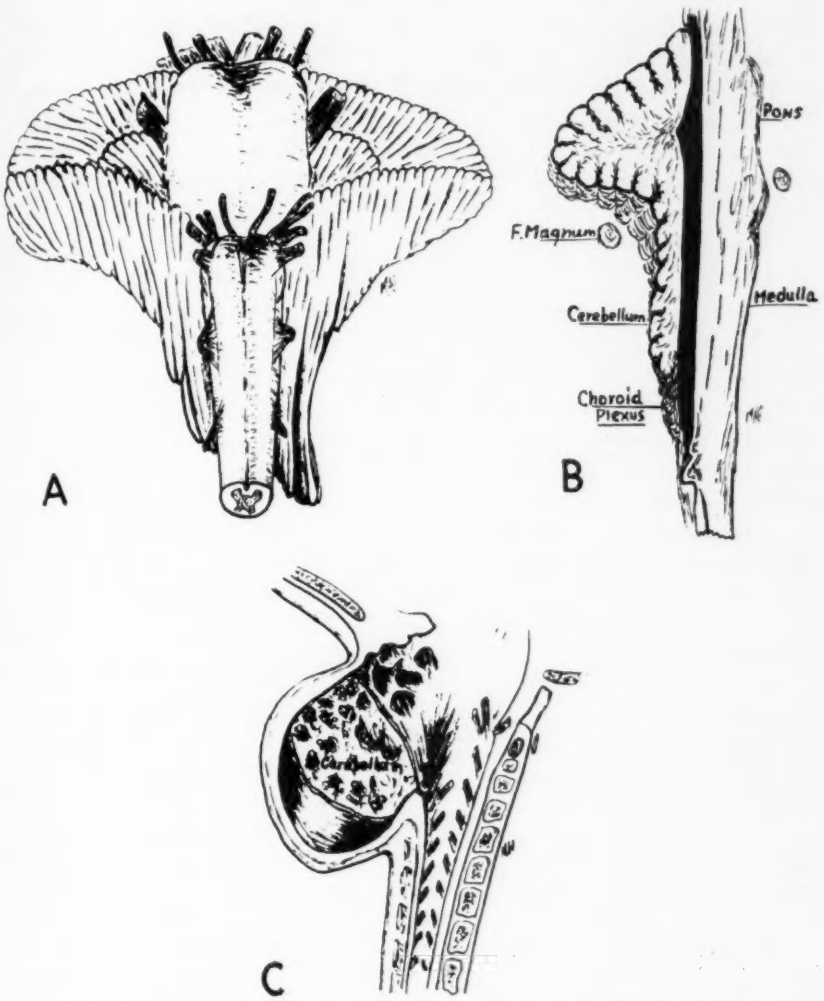

Fig. 1.—Diagrammatic sketches of malformations as classified by Chiari. (*A*) type 1; (*B*) type 2; (*C*) type 3.

5 month old infant with internal hydrocephalus, cervical spina bifida and myelomeningocele. Hydromyelia was frequently associated with all types.

In 1901 Solovtzoff [3] published a report of 5 cases of myelomeningocele with deformities of the hindbrain, in 3 of which a tonguelike process of cerebellum extended down into the vertebral canal, and in 1904 Sträussler [4] added a case. The most detailed account in the older literature is that of Schwalbe and Gredig,[5] in 1907, in which they described 4 cases of spina bifida with myelomeningocele. In 3 cases a tonguelike process of cerebellum was displaced downward into the upper part of the vertebral canal, carrying part of the fourth ventricle with it, while in the fourth case only the cerebellar tongue was present. Internal hydrocephalus was present in 2 cases but was absent in the others. The vermis of the cerebellum was either absent or rudimentary in every case.

Since these early publications the Arnold-Chiari malformation seems to have evoked little interest until the subject was revived by Russell and Donald's [6] excellent report in 1935 of 10 consecutive cases of spina bifida with myelomeningocele, in all of which the deformity described by Chiari, type 2, was present. Hydrocephalus was absent in 2 instances but was present in the other 8. The ages ranged from birth to 4 weeks. Subsequent studies of this deformity of the hindbrain have dealt particularly with the surgical treatment of the condition, varying degrees of success being reported.

The following 7 cases are reported to illustrate some of the varieties of the deformity that may be encountered.

REPORT OF CASES

CASE 1.—A full term female infant aged 4 days died after excision of a lumbar myelomeningocele.

Autopsy.—Lumbar spina bifida was associated with other congenital bony deformities, including multiple fused and bifid ribs and a small, maldeveloped right scapula. The cerebral hemispheres were considerably enlarged, as a result of internal hydrocephalus, while the cerebellum consisted of a small mass compressed from side to side, with its lower part extending through the foramen magnum and enveloping the dorsal aspect of the closed portion of the medulla. The fourth ventricle was not enlarged or displaced. The spinal cord tapered in the thoracic region, dividing at a lower level into two strands that encircled a bony projection from the body of the second lumbar vertebra. The left half presented hydromyelia of its central canal, extending down to the termination of

3. Solovtzoff, N.: Les difformités du système nerveux central dans le spina bifida, Nouv. iconog. de la Salpêtrière **14**:118, 1901; cited by Schwalbe and Gredig.[5]

4. Sträussler, E.: Ueber eine eigenartige Missbildung des Zentralnervensystems, Jahrb. f. Psychiat. u. Neurol. **25**:1, 1904; cited by Schwalbe and Gredig.[5]

5. Schwalbe, E., and Gredig, M.: Ueber Entwicklungsstörungen des Kleinhirns, Hirnstamms und Halsmarks bei Spina Bifida, Beitr. z. path. Anat. u. z. allg. Path. **40**:132, 1907.

6. Russell, D., and Donald, C.: The Mechanism of Internal Hydrocephalus in Spina Bifida, Brain **58**:203, 1935.

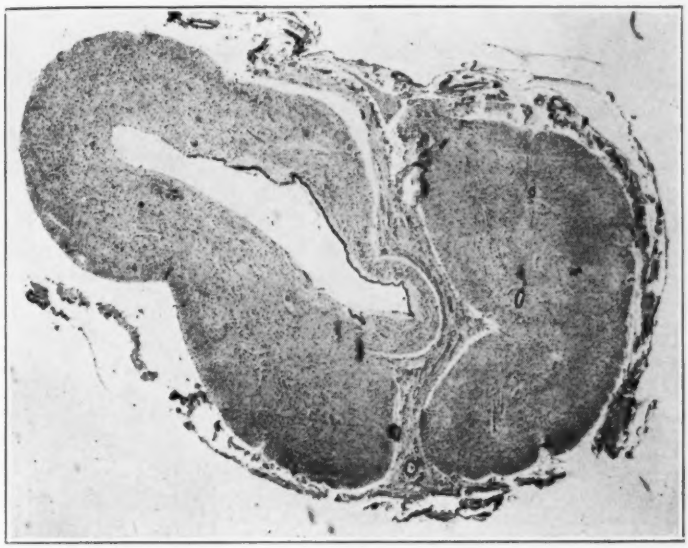

Fig. 2 (case 1).—Transverse section of lower lumbar portion of the cord. The central canal in the left half of the cord is tremendously dilated, while the right half of the cord contains two central canals, one of which lies within the posterior horn of the gray matter.

Fig. 3 (case 2).—Dorsal view of deformity of the medulla.

the cord, while two canals, each lined by ependyma, were present in the right half (fig. 2). The cauda equina was densely adherent to the floor of the meningocele sac.

CASE 2.—E. H., a full term male infant aged 32 days, was admitted to the hospital with hydrocephalus, lumbar spina bifida and meningocele. He died of meningitis.

Autopsy.—There was moderate enlargement of the cerebral hemispheres, with severe distention of both lateral ventricles. The fourth ventricle was slightly enlarged, but the cerebellum, although normal in size, showed no differentiation into vermis and lateral lobes. Overlying the dorsal aspect of the elongated medulla was a tonguelike fold of tissue, clearly demarcated by a deep groove and extending below the cerebellum for a distance of 1.5 cm. (fig 3). Microscopic examination showed that this dorsal tongue consisted of medulla, with a short fold of cerebellar tissue and choroid plexus at its upper extremity. There was no downward extension of the fourth ventricle, the foramens of which were located at the upper end of the deformity. No malformation was noted in the spinal cord apart from the infected meningocele sac.

CASE 3.—M., a girl aged 21 days, delivered at term by cesarean section, was admitted to the hospital with pronounced hydrocephalus and lumbar spina bifida with myelomeningocele. She died of spinal meningitis.

Autopsy.—Severe internal hydrocephalus involved the lateral and third ventricles. The midbrain was greatly stretched and narrowed, measuring 3.1 cm. in length on its ventral surface. This stretching was so prominent that the posterior end of the third ventricle was carried down into the upper portion of the midbrain and the basal ganglia appeared to have been drawn out of the ventral surface of the cerebrum, forming prominent masses at the upper ends of the cerebral peduncles. Overlying the dorsal surface of the upper part of the midbrain was a transparent, thin-walled cyst, 1.5 cm. in diameter, communicating above and ventrally with the cavity of the third ventricle. The colliculi were severely distorted, being compressed downward and from side to side. The pons was elongated, measuring 2.2 cm. in length, and caudal to the point of exit of the fifth nerve lay below the lower rim of the foramen magnum. The cerebellum was very small and somewhat cone shaped, without differentiation into vermis and lateral lobes. A considerable portion had herniated through the foramen magnum, forming a broad fold overlying the dorsal and lateral aspects of the open portion of the medulla to the level of the third cervical vertebra (fig 4). Thus the lower half of the pons, the medulla and a large portion of the cerebellum, with most of the fourth ventricle, were contained within the upper part of the vertebral canal. The choroid plexus was situated in the midline just below the tongue of cerebellar tissue, while the floor of the ventricle extended down for another 0.25 cm., its lower end being marked by a transverse crescentic fold on the dorsal surface of the closed portion of the medulla. All the cranial nerves were tremendously stretched. The third and fourth nerves took their origins within the cranial cavity; the fifth, at the level of the foramen magnum, while the rest emerged from the brain stem within the vertebral canal. They streamed upward over the ventral surface of the medulla and pons in order to reach the posterior cranial fossa (fig. 4*B*). The upper cervical nerve roots likewise were stretched and had a well marked upward inclination. Hydromyelia involving the central canal, the sac measuring about 2 cm. in length, was present in the upper cervical segments of the cord. Below this level the spinal cord was small and tapering, with its lower end incorporated in the wall

of the meningocele sac. The arachnoid and pia mater were densely adherent to one another and to the surrounding dura throughout the length of the vertebral canal. No deformities were noticed in the posterior cranial fossa or the upper cervical vertebrae.

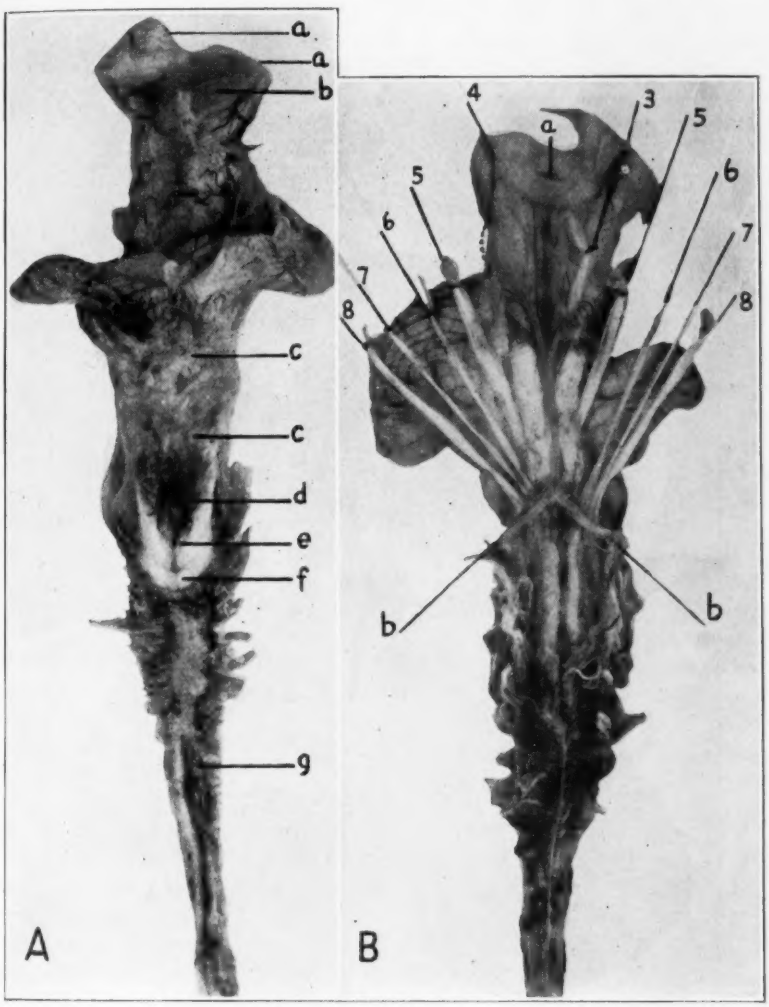

Fig. 4 (case 3).—*A*, dorsal view of deformity. Here, *a* indicates cerebral peduncles; *b*, transparent cyst overlying the midbrain; *c*, cerebellar tongue, clothed in filmy, adherent meninges; *d*, choroid plexus; *e*, lower end of floor of the fourth ventricle; *f*, crescentic fold of medulla; *g*, collapsed cord in region of hydromyelia.

B, ventral view of deformity. Here, *a* indicates opening into floor of the third ventricle; *b*, vertebral arteries; *3*, *4*, *5*, *6*, *7* and *8*, elongated cranial nerves stretched out by cotton threads.

Case 4.—W. A., a full term male infant aged 26 days, was admitted to the hospital with early hydrocephalus, cervical spina bifida occulta, lumbar spina bifida and lumbar meningocele. The meningocele sac was excised when the infant was 14 days old, death occurring twelve days later from meningitis.

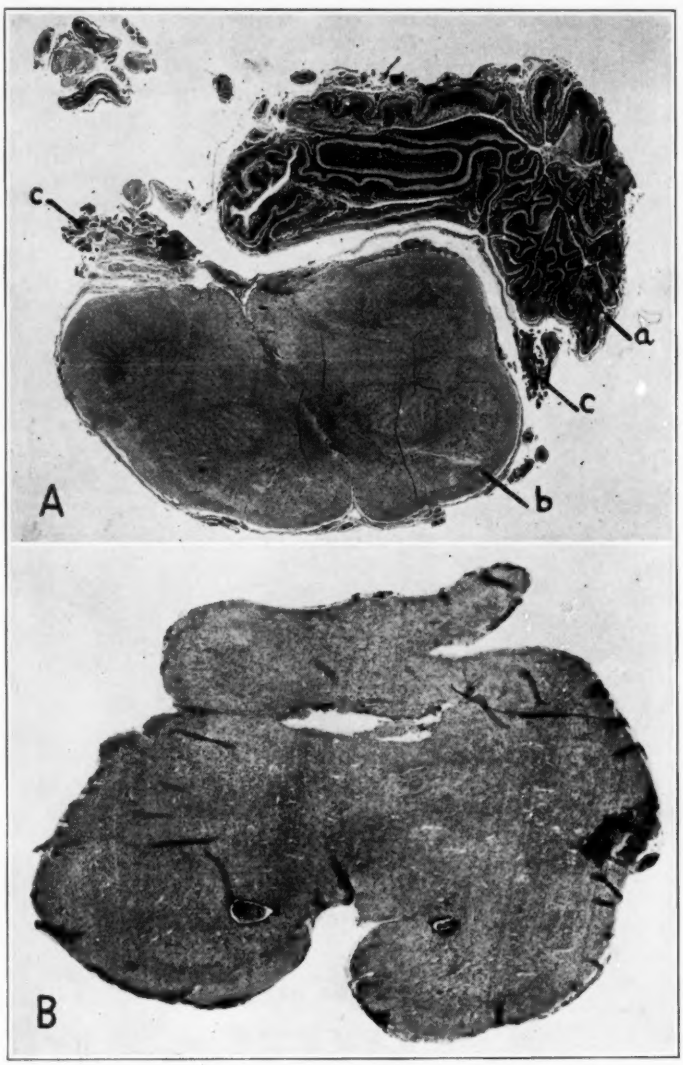

Fig. 5 (case 4).—*A*, transverse section through deformity at level of the inferior olive. Here, *a* indicates cerebellar tongue; *b*, medulla; *c*, choroid plexus.

B, transverse section through bulbous swelling at lower end of the cord, showing two central canals, each filled with purulent exudate.

Autopsy.—Examination confirmed a moderate degree of internal hydrocephalus involving the lateral and third ventricles. The cerebellum was smaller than normal and poorly differentiated, while a considerable portion of it extended through

the foramen magnum as a tonguelike mass and overlay the dorsal aspect of the medulla and upper cervical portion of the cord for a distance of 3 cm. A narrow fold of choroid plexus was carried down on either side of the tongue of cerebellar tissue. There were pronounced elongation and narrowing of the whole brain stem, so that the medulla and lower third of the pons, together with the greater part of the fourth ventricle, were contained within the vertebral canal. The relation of the structures is well shown in figure 5 *A*, a transverse section through the brain stem at the level of the inferior olive. All the cranial nerves with the exception of the first and second were considerably stretched, and those taking origin below the level of the pons streamed in an upward direction, passing through the foramen magnum to gain the cranial cavity. The spinal cord as it lay in the meningocele sac presented a bulbous expansion, measuring 1 cm. in diameter. A transverse section through this swelling showed two separate central canals, one on each side of the anterior median groove, lined by intact ependyma and filled with purulent exudate (fig. 5 *B*).

CASE 5.—W. N., a woman aged 23, was admitted to the Toronto General Hospital on Jan. 26, 1939, under the care of Dr. K. G. McKenzie.

History.—The patient was a domestic. Attacks of frontal headache began at the age of 19 years and occurred about once a week. The headache awakened her in the early morning and was usually followed by vomiting, even though no breakfast had been taken. It persisted all day, necessitating rest in bed, but generally cleared the following day. At the age of 21 amenorrhea developed, preceded by polyuria and precipitancy, and she was decidedly overweight. About four months before admission the headaches and vomiting became more severe, occurring at more frequent intervals and at any time of the day. There were attacks of severe suboccipital pain, with vertigo, diplopia, dysarthria, generalized trembling of the body and, sometimes, loss of consciousness. Hyperextension of the neck tended to relieve the pain, and while eating it was frequently necessary for her to stand in order to continue her meal. During the final two months before admission she noticed some staggering to either side and backward, the severity varying greatly from day to day.

Neurologic Examination.—Examination revealed loss of smell and papilledema bilaterally. There was no defect of the visual fields. The corneal reflexes were diminished, and there was subjective numbness over both sides of the face, more pronounced on the left side and worse during the attacks of pain. At times there were questionable nystagmus on looking to the left and weakness of the lower right side of the face. Sensation was diminished over the posterior wall of the nasopharynx and the soft palate. The tendon reflexes were sluggish but equal on the two sides. There was a tendency to stagger to either side and backward on standing and walking, particularly with the eyes closed. No evidence of involvement of the pyramidal tract was found. An area of tenderness was present at the level of the fourth cervical spine, but there was no spinal deformity. Stereoscopic roentgenograms of the skull showed thinning and "hammered silver" markings of the bones of the cranial box, with enlargement of the sella turcica and destruction of the posterior clinoid processes, but the defect in the sella was not that associated with pituitary tumor. A ventriculogram revealed marked dilatation of the lateral and third ventricles, with no lateral displacement.

The diagnosis was cerebellar tumor. The possibility of a chordoma was considered.

Operation (Feb. 10, 1939).—Bilateral cerebellar exploration, with removal of the arch of the atlas, disclosed pronounced herniation of the cerebellar tonsils through the foramen magnum, enveloping the posterior aspect of the closed portion of the medulla in the upper vertebral canal. There were some widening and retroplacement of the whole brain stem, with the midline shifted slightly to the left. The cerebellar deformity was bound down firmly by fine adhesions and was elevated only with difficulty, exposing the aperture of the fourth ventricle. The ventricular cavity extended to a lower level than normal, but not actually into the vertebral canal. As the left hemisphere was somewhat larger than the right and appeared a little soft, its upper and outer two thirds was resected. However, no tumor was found. After operation repeated attacks of stupor, relieved only by ventricular puncture, prompted a second exploration, and on February 23 the left cerebellar tonsil and the remaining lower third of the left hemisphere were resected. One-half the floor of the fourth ventricle was thus exposed, and at a higher level a cystlike structure was revealed, overlying the upper end of the midbrain. When opened this was seen to communicate with the third ventricle and appeared to be a backward projection of the dilated ventricular cavity. The patient did poorly after the operation and died three days later.

Autopsy.—Postmortem examination confirmed the severe internal hydrocephalus and well marked downward displacement of the remaining right cerebellar tonsil, which overlay the dorsal aspect of the closed portion of the medulla. The medulla was elongated and thinned out, as was also the fourth ventricle, but the lower end of this cavity was at the upper end of the herniated cerebellar tongue. No cyst was observed in the region of the aqueduct or pineal gland. The lower part of the spine was not examined for a possible deformity of the vertebral arches.

Case 6.—C. C., a man aged 38, was admitted to the Toronto General Hospital on Feb. 17, 1939, under the care of Dr. K. G. McKenzie.

History.—The patient, a school teacher, first noticed throbbing pain in the back of the neck in 1929, which was brought on by straining, as in stooping, coughing and sneezing, lasted only a few minutes and was always relieved by rest. The severity of the pain sometimes forced the patient to lie down at once. Shortly afterward he noticed that it was present when he awakened in the morning, lasting for approximately an hour and generally being localized about 1 inch (2.5 cm.) above the foramen magnum. The gradual increase in severity prompted him to seek medical advice in 1936, at which time the results of a neurologic examination were negative. In 1937 tingling developed in the fingers, hand and forearm on the right side; this was present constantly but was aggravated by bouts of suboccipital pain. He also became aware of increasing weakness of the legs, with marked instability on standing and walking, particularly in the dark. At the time of admission there was a constant burning sensation at the back of the neck and about the right ear.

Neurologic Examination.—The corneal reflex was diminished on both sides; there were some diminution of sensation in the distribution of the second division of the trigeminal nerve on the right side and complete loss of laryngeal sensation. There were fine rotary nystagmus on looking to either side and questionable papilledema in both fundi. The cranial nerves were otherwise normal. There was marked unsteadiness, both on standing and on walking, with a tendency to fall to the right, which was definitely worse with the eyes closed. No

involvement of the pyramidal tract was found. A ventriculogram showed no enlargement of the ventricular system, and there was no increase in intracranial pressure. No spinal deformity was noted.

The diagnosis was congenital herniation of the cerebellum.

Operation (Feb. 22, 1939).—A cerebellar exposure revealed such marked herniation of the cerebellum that it was necessary to remove the arches of the atlas and axis in order to expose the deformity. The tonsils and the medial parts of the inferior lobes of the cerebellum were elongated and carried down through the foramen magnum as broad folds enveloping the dorsal and lateral aspects of the medulla in the upper part of the vertebral canal and extending to the level of the lower border of the arch of the axis (fig. 6). When the

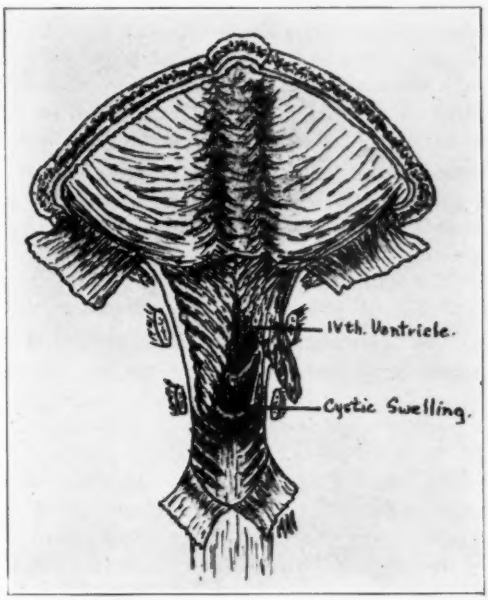

Fig. 6 (case 6).—Diagrammatic sketch of malformation encountered at operation.

cerebellar tongue was freed of adhesions and eased up, the lower end of the floor of the fourth ventricle was exposed down to the lower border of the arch of the atlas. Below this there was a soft cystic swelling on the posterior aspect of the lower end of the elongated medulla, overlapping the upper part of the cervical portion of the cord. It was felt that the fourth ventricle may have extended down into this swelling to the lower border of the arch of the axis.

The postoperative course was uneventful, but the patient continued to complain of some numbness and tingling in the fingers at the time of discharge from the hospital.

CASE 7.—C. P., a man aged 36, was admitted to the Toronto General Hospital on May 21, 1941, under the care of Dr. K. G. McKenzie.

History.—The patient, a laborer, one and a half years previously had first noted stiffness of the neck, with suboccipital pain and soreness high in the

cervical region on the right side. This was progressive, reaching its peak in the course of about a week and persisting without remission. The pain was aggravated by straining, as in coughing, sneezing and stooping, all of which gave rise to sudden severe generalized headache, blurred vision, diplopia, buzzing in the right ear and giddiness, with objects turning to the right. These attacks, during which he perspired profusely, lasted from one to two minutes. Staggering when walking, associated with a sensation of falling to the right, had been present for one year and some dysphagia for solid foods for two years.

Neurologic Examination.—There was no papilledema or defect of the visual fields. Diplopia was present in the right lower quadrant, with coarse horizontal nystagmus, more marked on looking to the right. Impairment of the corneal reflex, hypalgesia over the distribution of the trigeminal nerve and slight facial weakness were noted on the right, with some deviation of the jaw to that side. There was some suspicion of a nasal voice and deviation of the palate to the right. Tenderness was severe over the occipital bone, the mastoid process and the nuchal and temporal muscles on the right side, with atrophy of the muscles. The gait was a little clumsy, but there was no weakness of the extremities and no further evidence of sensory, reflex or motor involvement.

Diagnosis.—The clinical diagnosis was congenital herniation of the cerebellum. The possibility of platybasia was considered, since the odontoid process, as seen in lateral plates of the skull and cervical portion of the spine, appeared to be at a higher level than was believed normal, but there was no irregularity in the outline of the foramen magnum. The state of the ventricles is not known, as no ventriculogram was made.

Operation.—On June 13 a midline cerebellar exposure was performed, and it was found necessary to remove the arches of the atlas and axis to expose the deformity encountered. There was severe herniation of the cerebellum as a broad, massive fold overlying the medulla to the level of the axis and completely filling the dural space. As a result, the dorsal surface was deeply grooved by the arch of the atlas. The medulla was elongated, and the lowermost tip of the fourth ventricle was just visible immediately below the cerebellar tongue, while the lower part of the medulla and the upper cervical portion of the cord appeared enlarged, as though distended by the presence of hydromyelia. The arachnoid was split longitudinally over the tonsils, which were then eased gently out of the lower part of the fourth ventricle by dividing a few filmy adhesions. The dura was left open, with a muscle closure.

The symptoms improved after operation, but some nystagmus and headache still remain.

COMMENT

The Arnold-Chiari deformity must be regarded essentially as a congenital malformation, being present at or before birth. It is frequently found associated with other congenital anomalies and is subject to a considerable degree of variation.

As described by Chiari, the malformation consists of displacement of parts of the hindbrain through the foramen magnum into the upper part of the vertebral canal. The distinctive feature which generally enables its identification is a tonguelike fold of cerebellar tissue extending caudally through the foramen and overlying the medulla. This tongue

is of variable length but is always present to some degree, consisting usually of a median dorsal fold, or occasionally of two lateral folds embracing the posterolateral surfaces of the medulla. In some instances this alone may comprise the whole deformity, as in the first group described by Chiari and in cases 1 and 5 included here.

The more typical variety has, in addition, some elongation of the medulla, pons and, frequently, the midbrain, with variable portions of the medulla and pons lying within the spinal canal. The elongated fourth ventricle is carried down with the latter structures, so that its foramens are located below the foramen magnum. It may be hidden by the process of cerebellum but often extends to a lower level. The choroid plexus generally consists of a median mass situated at the lower end of the cerebellar tongue, or more rarely as two lateral masses, one on either side of it. Just below the lower limit of the open portion of the fourth ventricle there is usually a crescentic or tonguelike fold on the dorsal surface of the medulla, which overlaps the cervical portion of the cord and into which the cavity of the ventricle sometimes extends. Owing to the pronounced caudal displacement, the cranial nerves arising from the pons and the medulla are tremendously stretched, many of the lower roots arising below the foramen and streaming upward to reach the posterior cranial fossa. The same upward inclination is also present in the higher cervical nerve roots but diminishes in degree from above downward, the direction of the roots becoming horizontal in the lower cervical or upper thoracic segments. In the fresh specimen the whole deformity is usually invested in such dense and adherent membranes as to obscure anatomic landmarks to a considerable degree.

Frequently associated with the malformation are a variety of other anomalies, both developmental and acquired. When there is severe stretching of the brain stem the basal ganglia may be drawn down, forming prominent masses at the base of the cerebral hemispheres. Here the third ventricle extends into the upper part of the elongated midbrain, and sometimes its hindmost portion bulges backward, forming a cystic dilatation that overlies the quadrigeminal lamina. The colliculi tend to be poorly formed, being commonly fused into a single rounded elevation or a laterally compressed median ridge. The cerebellum is always small and poorly developed, without clear differentiation into vermis and lateral lobes. Spina bifida of some part of the vertebral canal is perhaps the most common accompanying developmental abnormality and is present in the large majority of cases. In some instances, however, there may be no demonstrable spinal deformity, as in the cases reported

by McConnell and Parker [7] and Aring [8] and in cases 5, 6, and 7 described here. When present it is usually associated with a myelomeningocele, but occasionally with a meningocele or spinal rachischisis. The spinal cord tends to be small and tapers caudally, commonly becoming incorporated at its lower end with the wall of the meningocele sac. Hydromyelia at some point is a frequent occurrence, as is also a splitting, or bifid condition, of the central canal (cases 1 and 4).

The question of hydrocephalus is an interesting one, particularly in regard to cause and effect. Although present in most instances, it is not an essential feature and does not necessarily develop even though the patient reaches adult life (case 6). As pointed out by Russell and Donald, the cerebrospinal fluid can as a rule pass readily from the displaced fourth ventricle into the spinal subarachnoid space. However, since the deformity is wedged into the foramen magnum after the fashion of a cork, the spinal fluid cannot get up around the brain stem to reach the cerebral subarachnoid space, where most of it is absorbed. This, then, would appear to be the explanation for the associated hydrocephalus in most cases. In some instances, however, as was noted post mortem in case 3, when the deformity fits tightly into the vertebral canal and is associated with dense adhesions, the fluid cannot escape from the fourth ventricle even when the deformity has been exposed by removal of the vertebral arches. It has been suggested that the fluid may then force its way down the central canal to produce hydromyelia. Whether hydrocephalus is responsible for the deformity in any of the cases is a question frequently advanced. Although increased intracranial pressure, with or without dilatation of the ventricular system, and from whatever cause, may produce herniation of portions of the cerebellum in the form of a pressure cone, rarely, if ever, does it produce a picture comparable to the malformation described. It is true that pressure from above, forcing the brain stem into the vertebral canal, would tend to produce elongation and narrowing of the structures within the canal in order to conform with the size and shape of that canal. On the other hand, it would not produce elongation and narrowing of the structures above the foramen, as is so frequently observed. This feature can more readily be accounted for on the basis of tension from below, particularly in the cases associated with spina bifida. Here the meninges, or meninges and spinal cord, are

7. McConnell, A. A., and Parker, H. L.: A Deformity of the Hindbrain Associated with Internal Hydrocephalus: Its Relation to the Arnold-Chiari Malformation, Brain **61**:415, 1938.

8. Aring, C. D.: Cerebellar Syndrome in Adult with Malformation of Cerebellum and Brain Stem (Arnold-Chiari Deformity), with Note on Occurrence of "Torpedoes" in Cerebellum, J. Neurol. & Psychiat. **1**:100, 1938.

intimately adherent to and incorporated with the wall of the sac and act as a point of fixation for the lower end of the cord. With the growth in length of the vertebral column, traction is exerted on the spinal cord and its enveloping membranes and, through these structures, on the brain stem. Since this same bag of membranes is intimately attached to the cerebellum, the latter is likewise drawn downward. Such a mechanism would produce stretching of the whole brain stem, including the structures above the foramen. The explanation is also in accord with the observation by Penfield and Coburn [9] that a wide space occurred between the upper surface of the cerebellum and the tentorium and that the cerebellum retracted after operative dissection of adhesions. Remaining to be explained, however, are those cases in which the condition is not associated with spina bifida, and it would be interesting in such cases to search for a possible attachment of the spinal cord or its membranes to the bony wall of the vertebral canal.

The classification of the malformations into types 1 and 2 according to the degree of displacement appears to be a good one, particularly as it eliminates the arbitrary dividing line between what is and what is not a true deformity. The feature differentiating the first and the second type is of course the position of the fourth ventricle as governed by the elongation of the brain stem. There is no marked retroplacement of the ventricle in the first type, whereas in the second a variable portion of its lower end, with the foramens, is contained within the upper portion of the vertebral canal. The third type is obviously of no practical importance.

In most of the cases in the literature the condition occurred in infants in association with spina bifida and internal hydrocephalus, but of late an increasing number of occurrences in adults have been reported. It is only reasonable to expect that those patients surviving to adult life would tend to present a milder degree of the deformity, children with the more severe types dying at an early age.

In the recent literature there have appeared examples of herniation of portions of the cerebellum associated with craniovertebral deformities, in particular basilar impression (platybasia). Here the floor of the posterior cranial fossa is pushed up and flattened, the foramen magnum is small and misshaped or eccentric and the atlas is commonly fused as a whole or in part to the occipital bone. As a result, there is compression of the medulla by the stenosed foramen, while the odontoid process of the axis projects into the uppermost part of the spinal canal, frequently impinging on the brain stem. Gustafson and Oldberg [10] described 2 such

9. Penfield, W., and Coburn, D. F.: Arnold-Chiari Malformation and Its Operative Treatment, Arch. Neurol. & Psychiat. **40**:328 (Sept.) 1938.

10. Gustafson, W. A., and Oldberg, E.: Neurologic Significance of Platybasia, Arch. Neurol. & Psychiat. **44**:1184 (Dec.) 1940.

cases, in 1 of which herniation of the right cerebellar tonsil below the arch of the atlas was noted and in the other herniation of both tonsils to the arch of the axis. Walsh and associates [11] reported a similar case with herniation of the tonsil of the right cerebellar lobe to the level of the third cervical vertebra. In all these case reports no mention was made of the position or possible displacement of the fourth ventricle.

What relation exists between basilar impression and the Arnold-Chiari deformity is not yet clearly understood, but it may well be merely one of association of congenital abnormalities, since this frequently occurs (case 1). The herniation is not always present in cases of basilar impression, and it is difficult to conceive how the bony deformity could produce such displacement of cerebellar tissue except on a developmental basis. In each condition there is compression of the structures at the foramen magnum, with a tendency toward obstruction of circulation of the cerebrospinal fluid. Internal hydrocephalus and dilatation of the central canal of the cord commonly result.

SYMPTOMS

The symptomatology of the Arnold-Chiari deformity in the adult is varied and inconstant. Tumor of the cerebellum or the posterior cranial fossa is the most common preoperative diagnosis, and it is usually not until exposure is made that the true nature of the lesion is realized. Early morning headaches, ataxia of the cerebellar type with staggering to either side or backward, nystagmus, palsies of the cranial nerves, visual disturbances, papilledema and vomiting may all be present to a varying degree. The headache, papilledema and vomiting are dependent on the presence of increased intracranial pressure, while the ataxia and palsies of the cranial nerves seem to result from direct compression of cerebellar tissue and involvement of the nerves. This is understood in cases in which there is marked retroplacement and the lower cranial nerves take origin below the foramen magnum. Pain in the occipital, suboccipital or high cervical region, due to compression of the upper cervical nerve roots, with, frequently, paresthesias in the upper extremities, may be a prominent feature, and it is significant that the pain can sometimes be relieved by stretching or forward flexion of the neck. Occasionally it may be the patient's only complaint, dating back for a considerable number of years. The distinct tendency for the signs and symptoms to show considerable variation from day to day, together with the relief offered by rest in bed and their aggravation on coughing and

11. Walsh, M. N.; Camp, J. D., and Craig, W. McK.: Basilar Invagination of the Skull (So-Called Platybasia): Report of a Case with Operation, Proc. Staff Meet., Mayo Clin. **16**:449, 1941.

straining, points to something jamming the foramen magnum. Associated with an old operative scar for spina bifida or signs of spina bifida occulta, these symptoms should always make one suspect the malformation. A similar clinical picture may occur in cases of platybasia, but frequently there are additional features that are not commonly encountered in cases of the Arnold-Chiari deformity. A true syringomyelic state of the bulb and cervical portion of the cord may be present, with dissociation of touch, pain and temperature sensibility over the affected area. Owing to the compression of the medulla by the odontoid process and the margins of the stenosed foramen, signs of involvement of the sensory and motor tracts are common and often simulate other neurologic conditions, such as disseminated sclerosis and spastic spinal paralysis.

TREATMENT

The operative treatment resolves itself into one of decompression over the deformity and reestablishment of the cerebrospinal fluid circulation. Enlargement of the foramen magnum with removal of the arches of the upper two or three cervical vertebrae may be all that is necessary. If, owing to dense meningeal adhesions, this does not restore the normal circulation of the fluid, incision of the arachnoid either in the midline or on each side of the tongue of cerebellar tissue may be required. Too free mobilization of the tongue is inadvisable and should not be necessary, while resection of any portion of it is decidedly a dangerous procedure. In cases of spina bifida, either with meningocele or with meningomyelocele, the possible presence of the deformity must always be kept in mind, particularly if hydrocephalus appears to be imminent after operative closure. The practical application of this point is remarkably well illustrated in a report by D'Errico [12] on a series of 10 cases of spina bifida with myelomeningocele. It is of the utmost importance that the neural tissue and membranes, including the dura, be dissected free of any attachment to the bony vertebral canal, in this way relieving possible fixation and traction on the cord.

SUMMARY

A general study of the Arnold-Chiari malformation is presented, with a short series of illustrative cases. Of these, 3 were of adults and operation was performed, with 1 fatality. In cases 6 and 7 the presence of the deformity was suspected before operation and was confirmed at operation.

12. D'Errico, A.: Surgical Procedure for Hydrocephalus Associated with Spina Bifida, Surgery **4**:856, 1938; The Surgical Treatment of Hydrocephalus Associated with Spina Bifida, Yale J. Biol. & Med. **11**:425, 1939.

Emphasis is placed on the wide anatomic variations that may be encountered, and it is suggested that the cases be grouped under two types. In the first type there is no displacement of the fourth ventricle, and in the second a portion of the ventricular cavity is contained within the vertebral canal. This feature is a direct indication of the degree of elongation or stretching of the brain stem and points to one of the causative factors in the abnormal development, viz., fixation of the spinal cord or its enveloping membranes to the bony vertebral canal at some point, with resultant stretching in many instances. A few of the associated developmental anomalies are mentioned, including platybasia, in which interest has recently been revived. The clinical aspects of the malformation, with the operative treatment, are discussed briefly.

Dr. E. A. Linell, Professor of Neuropathology, University of Toronto, gave valuable assistance in the preparation of this report, and Dr. K. G. McKenzie, Toronto General Hospital, and Dr. I. H. Erb, Hospital for Sick Children, permitted me to include their cases.

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EFFECT OF ROTATION ON POSTURAL STEADINESS IN NORMAL AND IN SCHIZOPHRENIC SUBJECTS

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Vestibular reactivity in schizophrenic patients has been investigated by several experimenters,[1] who have in general found that after caloric or rotatory stimulation nystagmus was absent or diminished as compared with the response in normal subjects. Angyal and Blackman,[2] in a recent and more elaborate study, confirmed this observation on 58 patients and 20 normal subjects.

Our purpose in the present study was to determine whether such lesser reactivity in the vestibular apparatus was accompanied by any changes in the muscle tonus as related to postural activity. The effect of rotation on standing steadiness was therefore investigated in normal and in schizophrenic subjects.

METHOD AND MATERIAL

Subjects.—The subjects included 30 normal persons and 30 healthy male schizophrenic patients. The nonpsychotic, control subjects were drawn from the personnel of the hospital and from students at a nearby university. Their ages ranged from 18 to 36, the average being 22 years. The schizophrenic subjects were selected at random from the research service ward of the hospital; their ages ranged from 20 to 48, the average being 32 years. The patients had been hospitalized for periods ranging from one month to fifteen years, the average being four and one-tenth years. They included all the recognized subtypes of schizophrenia.

Procedure.—The procedure consisted essentially of determining the steadiness in standing of the subject before and after rotation. This steadiness was measured by means of strings attached to a belt around the waist, which were connected to heated levers marking on a waxed paper kymograph. One string was attached

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From the Memorial Foundation for Neuro-Endocrine Research and the Research Service of the Worcester State Hospital.

1. Claude, H.; Baruk, H., and Aubry, M.: Contribution à l'étude de la démence précoce catatonique: Inexcitabilité labyrinthique au cours de la catatonie, Rev. neurol. **1**:976-980, 1927. Joó, B., and von Meduna, L.: Labyrinthreizungsuntersuchungen bei Schizophrenie, Psychiat.-neurol. Wchnschr. **37**:26-29, 1935.

2. Angyal, A., and Blackman, N.: Vestibular Reactivity in Schizophrenia, Arch. Neurol. & Psychiat. **44**:611-620 (Sept.) 1940.

anteriorly in the midline and the other laterally on the left. Any degree of swaying was transmitted by the movement of the strings to the markers. The anterior string reflected primarily anteroposterior movements and the lateral string side to side movements, although in each case some degree of movement in the other plane was shown. The extent of the vertical deviations of the waves from a given starting point was measured by means of a Hull oscillometer.[3] The amount of these deviations per minute in both the anterior and the lateral plane was added to give the total deflection in all directions. The figure obtained, therefore, represented movement in all planes expressed in arbitrary units. It should be noted that any value given represents a degree of unsteadiness and is called hereafter unit of sway.

The rotation was done in a chair suspended from a drum revolving by means of a ball-bearing joint in the ceiling. The drum (and consequently the chair) was turned by means of pulleys driven by a crank arrangement. A bicycle speedometer attached to the rim of one of the pulleys indicated the speed of revolution of the chair. An adjustable head rest was attached to the back of the chair, so that during rotation a fixed, upright position of the head was maintained. A heavy spring running from a universal joint in the floor to the bottom of the chair limited its lateral excursion during rotation.[4]

The experiment was carried out at least two hours after a meal in order to minimize gastrointestinal disturbances incident on the rotation. After the subject was seated in the chair the head rest was adjusted. Dark glasses were worn to prevent the fixation of vision, with its influence on steadiness. The subject then slid down onto a stand, and the strings were attached to a belt around his waist. The height of this stand could be adjusted to maintain the distance of the belt from the ground approximately the same in all cases, so that the strings were always in the same horizontal plane. A control record of the standing steadiness was first obtained for at least four minutes. The strings were then detached, and the subject sat on the chair again. After a rest period of three minutes rotation of the chair began. The speed of rotation was quickly increased so that the maximum speed used (1 rotation in one and two-thirds seconds) was reached in fifteen seconds and maintained for two minutes. The rotation was then stopped abruptly, and the subject again slid off the chair onto the stand as rapidly as possible. The strings were reattached to the belt, and a record was again taken of his steadiness during the next four minutes. The interval between the cessation of rotation and the beginning of the recording of movement was noted on the kymograph.

RESULTS

The reaction of the subjects to rotation varied widely. In some instances there was no apparent dizziness and the subject stood up promptly. In most of the cases, however, the subject was so unsteady

3. Hull, C. L.: An Instrument for Summating the Oscillations of a Line, J. Exper. Psychol. **12**:359-361, 1929.

4. In order to ascertain the autonomic responsiveness of the subject, the heart rate and skin conductance were measured continuously throughout the procedure. The results will be discussed in another paper (Rodnick, E. H., and Freeman, H.: The Effect of Rotation upon Heart Rate and Skin Conductance in Schizophrenic and Normal Subjects, to be published).

that he had to be helped out of the chair and supported for a short time. As the recording was started when the subject could stand unaided, there was inevitably some variation in the interval between the stopping of rotation and the beginning of the record.

For the whole group of 30 normal subjects the average interval was twenty-eight seconds and for the 30 patients thirty-one seconds. As the reaction was but a transitory one and as this difference might possibly affect the results, it was decided to confine the analysis of the data to a group of normal controls for whom this interval was the same as for the patients. Accordingly, the control and the psychotic subjects were

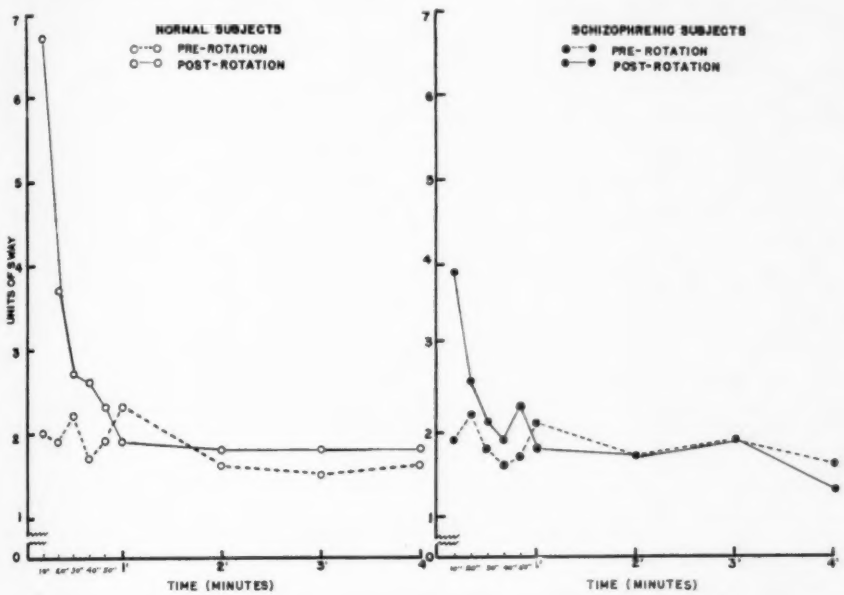

Fig. 1.—Means of unsteadiness (units of sway) measured every ten seconds during the first minute of recorded standing and every minute thereafter for a total duration of four minutes, before and after rotation on 17 normal and 17 schizophrenic subjects.

matched for time intervals without regard to the amplitude of the reaction. It was found possible to do this with 17 pairs of subjects, and it is to this number that we shall limit the discussion.

The effect of the procedure on the postural stability of the subjects is shown in figure 1. Each point represents a mean value for 17 subjects, either patients or normal controls, in the prerotational and the postrotational period. In the graph on the left are the values for the normal subjects, while that on the right shows the figures for the patients. Since

the reaction was a transitory one, the first minute was measured in ten second intervals and subsequent minutes as wholes. The values for the last three minutes were divided by 6 to obtain an average value for ten seconds which would correspond to those obtained during the first minute.

Examination of the figure shows that the prerotational values for the normal group expressed in units of sway for the first minute are higher than those for subsequent minutes, which may be assumed to be due to the adjustment in muscle tonus in changing from the sitting to the standing position, with a later relaxation as balance is more easily maintained. The corresponding points after rotation show a rise of the

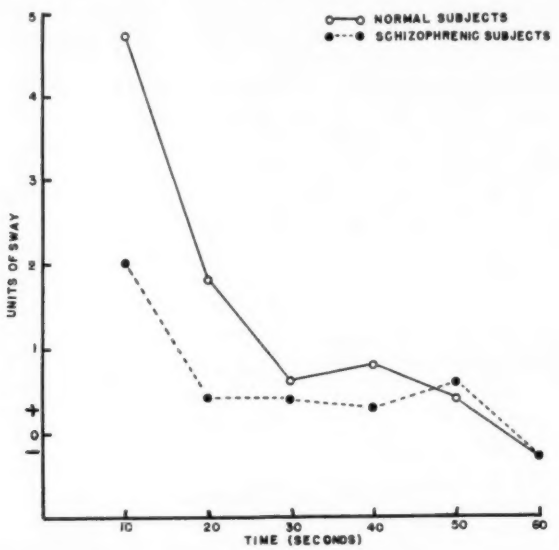

Fig. 2.—Mean differences in sway for each ten seconds of the first minute of recorded standing before and after rotation for 17 normal and 17 schizophrenic subjects.

initial value from 2.01 to 6.66 and of the second reading from 1.91 to 3.69. Subsequent differences are slight, and it may be said that the unsteadiness is essentially over after twenty seconds of recording. Indeed, only the first two points show a difference that is statistically significant.

Turning to the patients, it is seen that the values for the prerotational readings are essentially at a more stable level. There is less fall from the first to the second minute than in the case of the normal controls, which may be due either to the less vigorous shift from the chair to the stand or to their greater unconcern with the situation as a whole. Their values during the first minute are slightly lower than those for the normal

subjects, but on the whole in the unstimulated situation there is little difference between the two groups. After rotation the initial value increases from 1.90 to 3.90, which was found to be statistically significant. The increase is, however, much less than that for the normal subjects, the difference also being statistically significant. Subsequent readings, prerotational and postrotational, are quite similar. In addition, the postrotational readings during the last three minutes are approximately the same as those for the normal subjects, so that it may be said that whatever differences are present between normal and schizophrenic subjects are to be found within the first minute of recording.

Increases in Unsteadiness (Units of Sway) of the Postrotational Over the Control Values for the First Ten Seconds of Recorded Standing for Seventeen Pairs of Subjects (Normal and Schizophrenic) Matched for Time Intervals Between Cessation of Rotation and Onset of Recording

Normal Subjects		Schizophrenic Subjects	
Time Intervals, Seconds	Increase In Sway, Units	Time Intervals Seconds	Increase In Sway, Units
45	7.75	44	0.50
35	3.80	34	2.25
35	5.45	34	0.00
30	1.50	30	0.35
30	7.30	30	−0.90*
30	6.25	31	0.60
30	11.30	29	2.70
25	1.75	27	1.65
25	0.00	27	0.25
24	−1.50*	26	6.40
24	3.25	26	6.05
24	1.35	24	2.60
24	6.10	24	6.90
23	3.05	23	−0.90*
22	7.10	22	3.20
22	2.10	21	0.70
21	12.50	21	1.10
Mean 27.6	4.65	27.8	1.96
Difference between mean rise for normal controls and that for patients			2.69
Standard deviation of this difference			±1.00
Critical ratio of this difference			2.69
Probability of this difference			<0.01

* Postrotation value smaller than the control value.

This is shown clearly in figure 2. Here are the differences between the prerotational and the postrotational means for each of the ten second intervals in the first minute of recorded standing for the normal and the schizophrenic subjects. The values for the normal subjects are significantly higher only for the first twenty seconds. At the onset of recording, for the first ten seconds, the difference between the two groups is highly significant, having a probability of less than 0.01. At the twenty second period the difference between the two groups is considerably less, and at the subsequent periods the values are essentially similar.

Since the reaction is of such a transitory nature, it is necessary to consider carefully the factor of the time interval between the cessation of the rotation and the onset of recording. The table shows the results

obtained in the individual cases by the technic of matching. For 7 pairs the times were absolutely the same; for 6 pairs the difference was one second, and for 4 pairs, two seconds. The matching was done by random selection, so that no temporal bias was exercised for either group. The average time interval for the normal subjects was twenty-seven and six-tenths seconds and for the patients twenty-seven and eight-tenths seconds. It is evident, therefore, that the time intervals for both groups were essentially identical and that the differences shown in figure 2 are, from this point of view, reliable.[5]

Analyses were made with regard to determining possible relations with the type or duration of the psychosis. Since the normal group was 10 years younger on the average than the patients, a correlation was made between age and the increase in unsteadiness in both groups to determine what influence this factor might have on the difference in reaction between the two groups. No relation was found, however, so that the greater age of the patients does not play a role in their lesser reactivity.

The chronicity of the disease as measured by the length of hospitalization does not seem to be related to the reactivity of the schizophrenic group. One third of the group had been hospitalized for less than one year, and their values extended over at least as great a range as those of the patients who had been institutionalized for the longer periods.

Nor was any relation found in general between the subtypes of schizophrenia and the degree of increase in unsteadiness. The catatonic group tended to have higher values, but their small number (3 cases) makes it unwise to draw any conclusions on this point.

COMMENT

To which factors may be ascribed the lesser reactivity of the vestibulospinal mechanisms is unknown. The results, however, are in accord with those dealing with nystagmus.[2] On the basis of the present experiment, however, it is impossible to determine with any degree of assurance the exact nature of the lesser responsiveness of

5. For the entire group of 60 subjects the average time interval was twenty-eight seconds for the control subjects and thirty-one seconds for the psychotic subjects. Consequently, one would ordinarily expect that this greater delay in the onset of recording in the patient group would lead to a slighter reaction. In the larger group the mean rise in the first ten seconds is 4.47 for the normal subjects and 2.31 for the patients, a difference of 2.16. This difference is statistically significant and is essentially the same as that obtained for the 17 pairs of subjects matched for time, i. e., 2.69 (table). Consequently, we may assume that this phenomenon of lesser reactivity holds equally for the entire group and cannot be the result of the difference in the intervals.

the schizophrenic patient. Several alternative explanations suggest themselves. On the one hand, the lesser reaction of the schizophrenic group may be a result of a fundamental deficiency in the response of the vestibular and higher neural mechanisms to postural stress. But, on the other hand, considerable weight must be given to the possibility that the major factor in accounting for the differences in response between normal and schizophrenic persons may be the postural substrate on which the unsteadiness reaction is superimposed. Although during the control period before rotation both groups showed the same degree of unsteadiness, it is quite possible that unsteadiness during ordinary standing conditions is not an adequate measure of such a complex mechanism as postural tonus. Until the effect of rotation on postural tonus per se is measured by more direct means, any hypothesis as to the probable nature of the deficiency in the schizophrenic patient should be kept in abeyance. Whatever the background, it fits into the picture of generally lessened physiologic responsiveness found in the majority of schizophrenic patients.[6]

CONCLUSION

On 30 normal and 30 male schizophrenic patients a study was made of the amount of sway induced by rotation. It was found that the patients were significantly less reactive to the stimulus than were the normal subjects.

6. Angyal, A.; Freeman, H., and Hoskins, R. G.: Physiologic Aspects of Schizophrenic Withdrawal, Arch. Neurol. & Psychiat. **44**:621-626 (Sept.) 1940.

PROGRESSIVE DEGENERATIVE ENCEPHALOPATHY

OCCURRENCE IN INFANCY, WITH ANTENATAL ONSET SIMULATING "SWAYBACK" OF LAMBS; REPORT OF A CASE

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The data reported here may prove to be of importance in throwing additional light on the problem of Schilder's disease and related demyelinating or degenerative encephalopathies. It may also help to explain some of the clinical syndromes often attributed to birth trauma.

"Swayback" in lambs has been shown by Innes and Shearer [1] to be of antenatal development, and even in those cases in which the condition was manifested at a considerable time after birth the defect probably began in utero. Innes and Shearer stated that "rarely only one of twin lambs was observed to be affected at birth, but in such cases the other often showed symptoms later in life. When only one of twin lambs is visibly affected at birth we do not know whether the other lamb remains permanently free from symptoms."

There are many clinical and pathologic similarities between "swayback" and Schilder's disease, the latter being considered in the main as a postnatal disturbance. Mackay [2] reported 3 cases of what he termed congenital demyelinating encephalopathy, in which he asserted that the pathologic process was present from birth. His patients were older than the infant whose case is presented here and the pathologic changes less severe.

From the John L. Eckel Laboratory of Neuropathology, University of Pennsylvania Graduate School of Medicine, and the Jewish Hospital.

Read at the meeting of the American Association of Neuropathologists, June 9, 1941, at Atlantic City, N. J. An abstract of this paper, with discussion, appeared in the transactions of the society published in the February 1942 issue of the ARCHIVES, page 345.

1. Innes, J. R. M., and Shearer, G. D.: "Swayback": A Demyelinating Disease of Lambs with Affinities to Schilder's Encephalitis in Man, J. Comp. Path. & Therap. **53**:1, 1940.

2. Mackay, R. P.: Congenital Demyelinating Encephalopathy, Arch. Neurol. & Psychiat. **43**:111 (Jan.) 1940.

The many human forms of demyelinating and degenerative encephalopathy, such as Schilder's disease,[3] Krabbe's disease,[4] Pelizaeus-Merzbacher disease,[5] "encephalitis congenita" of Virchow[6] and the encephalopathies described by Hermel,[7] Flatau[8] and others, have certain pathologic similarities, which led Ferraro[9] to endeavor to harmonize the divergent concepts regarding them. Ferraro expressed the belief that the different types of demyelinating disease encountered depended essentially on the age at which the disease made its appearance, the distribution of the lesions, the degree of original involvement and rapidity of progression and, finally, the resistance of the tissues.

Globus and Strauss[10] stated the opinion that distinctions between the various demyelinating diseases should be made on the basis of the primacy of the histopathologic process, i. e., whether demyelination or gliosis is the primary manifestation.

In the absence of definitive knowledge of the etiology and interrelation of the various demyelinating diseases, the case presented here, with its pathologic aspects combining diffuse, symmetric subcortical demyelination with intense cortical and subcortical gliosis, together with the clinical and pathologic resemblances to "swayback," may serve as a

3. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose (Ueber Encephalitis periaxialis diffusa), Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912.

4. Krabbe, K.: Beitrag zur Kenntnis des Frühstadien der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **20**:108, 1913.

5. Pelizaeus, F.: Ueber eine eigenthümliche Form spastische Lähmung mit Cerebralerscheinungen auf hereditärer Grundlage (multiple Sklerose), Arch. f. Psychiat. **16**:698, 1885. Merzbacher, L.: Eine eigenartige familiärhereditäre Erkrankungsform (Aplasia axialis extracorticalis congenita), Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1, 1910.

6. Virchow, R.: Kongenitale Encephalitis und Myelitis, Virchows Arch. f. path. Anat. **38**:129 1867.

7. Hermel H.: Ueber einen Fall von Encephalomyelomalacia chronica diffusa bei einem vierjährigen Kinde, Deutsche Ztschr. f. Nervenh. **68**:335, 1921.

8. Flatau, E.: Encephaloleucopathia scleroticans progressiva, Encéphale **20**: 475, 1925.

9. Ferraro, A.: Primary Demyelinating Processes of the Central Nervous System, Arch. Neurol. & Psychiat. **37**:1100 (May) 1937.

10. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy (Schilder's Disease), Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

unifying nexus between the diverse views on the demyelinating diseases and related conditions.

REPORT OF CASE

J. K., a white female infant was delivered at full term in the Jewish Hospital on Nov. 27, 1940, the first child of normal, non-Jewish parents, aged 24 and 25 respectively. Her weight was 7 pounds (3,175 Gm.). She was transferred to the pediatric service of Dr. A. Dannenberg, where she died twelve weeks later.

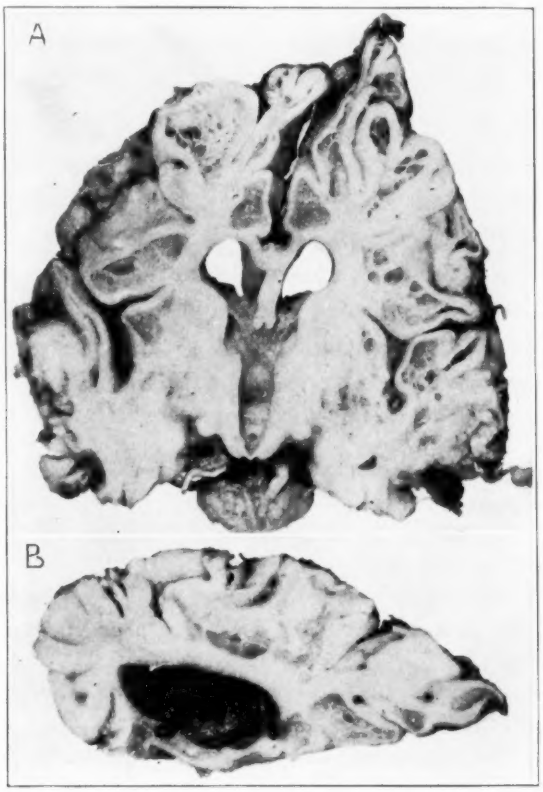

Fig. 1.—*A*, coronal section, showing diffuse, symmetric cystic cavitation of the cerebral white matter, with a thin shell of cortex remaining. Note the dilated ventricular system.

B, section through the occipital lobe, showing cystic cavitation of the white matter and hemorrhagic enlargement of the choroid plexus.

After a prolonged labor resuscitation of the infant was difficult, requiring the use of carbon dioxide and oxygen. On the day after birth the temperature was 99.3 F., and the respirations were rapid but regular; she lay passive with occasional sucking movements of the lips. Mild hypertonus was present. The

eyes were closed, and the pupils were miotic and equal. On November 30 she would not suckle and cried occasionally in a high-pitched tone; the anterior fontanel was tense, and the extremities were rigid. Spinal puncture showed a pressure of 300 mm. of cerebrospinal fluid, and the fluid was bloody. The temp-

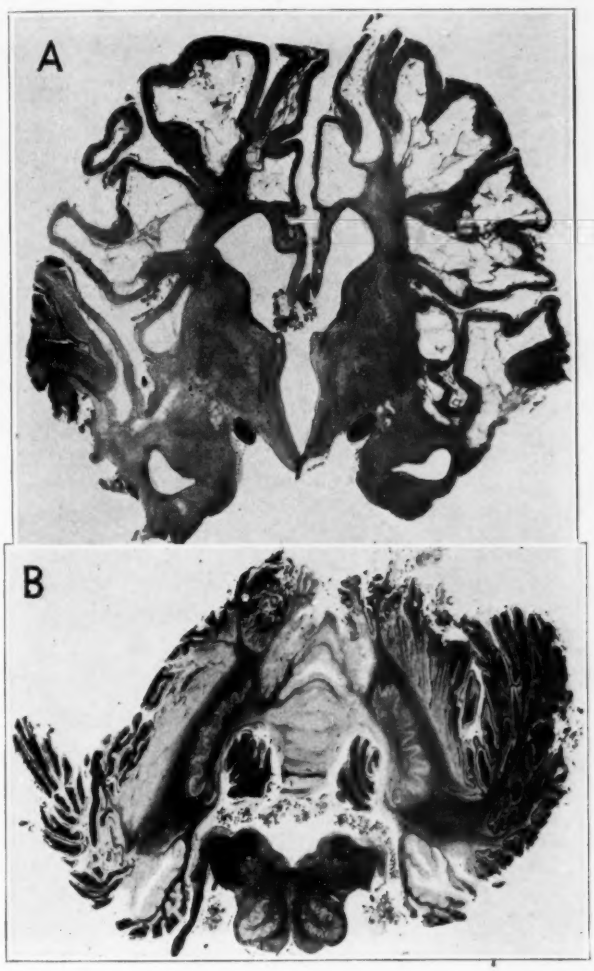

Fig. 2.—*A*, complete demyelination of the white matter. The optic tracts show preserved myelin.

B, partial demyelination of the cerebellum. The extent of myelination within the medulla is demonstrated.

Weil stain for myelin sheaths; × 2.

erature rose to 104 F. On December 1 convulsions made their appearance and were present at intervals until death. On December 27 the fontanels were very

tense and the cranial sutures were widened. The swallowing reflex was absent, and vomiting frequently followed tube feedings. On Jan. 27, 1941 a generalized eczema appeared. The neurologic findings at this time were hyperactive tendon reflexes, intense rigidity of the limbs, a bilateral Babinski sign, convulsive movements and absence of the swallowing reflex. Serologic studies gave negative

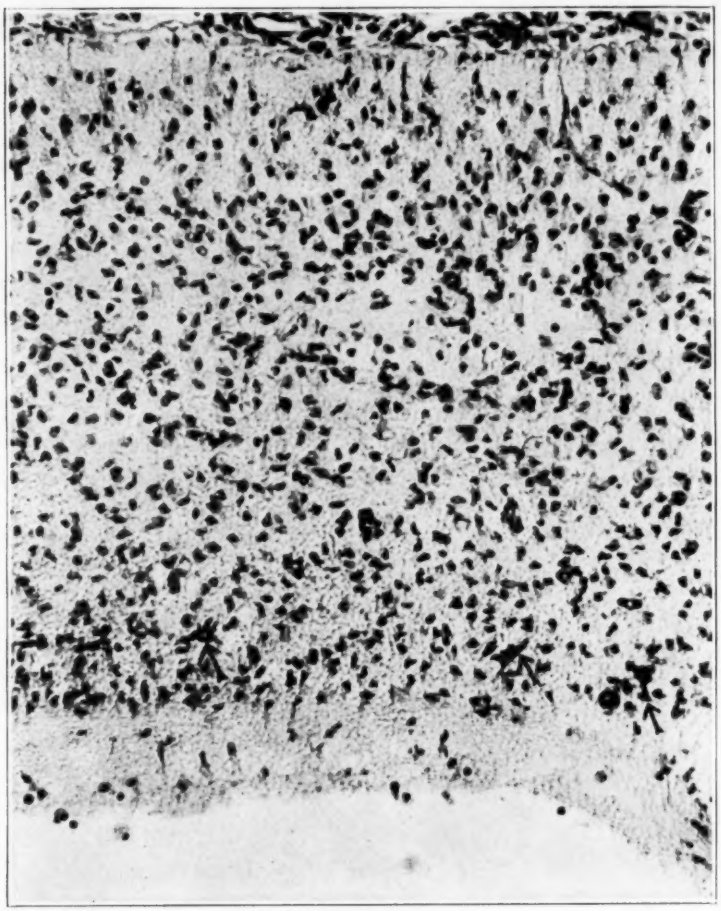

Fig. 3.—Section through the cerebral cortex, showing immature neurons and calcified ganglion cells (indicated by arrows). Note intense astrocytic gliosis and accumulation of gitter cells. Toluidine blue; × 200.

results. The child died on February 18, at the age of 12 weeks. At autopsy death was found to be due to bronchopneumonia, purulent meningitis and marasmus.

Gross Appearance of the Brain.—The brain was extremely small. The leptomeninges were fluffed out and loosely adherent to the cortex, the surface of which

appeared and felt gelatinous. Throughout the brain the gyri were small, and in the parietal lobe of each hemisphere, particularly the left, they were arranged in accordion-like fashion. Sections through the medulla and cerebellum revealed the tissue to be somewhat gelatinous, whereas the pons gave increased resistance on sectioning. Coronal section through the frontal lobes showed cystic gelatinous degeneration of the greater part of the subcortex. Some of the cystic cavities contained an opalescent liquid rather than gelatinous material. The cortex was thinned out so that in some parts only a thin shell of cortex remained. Coronal sections proceeding caudally revealed the subcortex of some areas to be completely

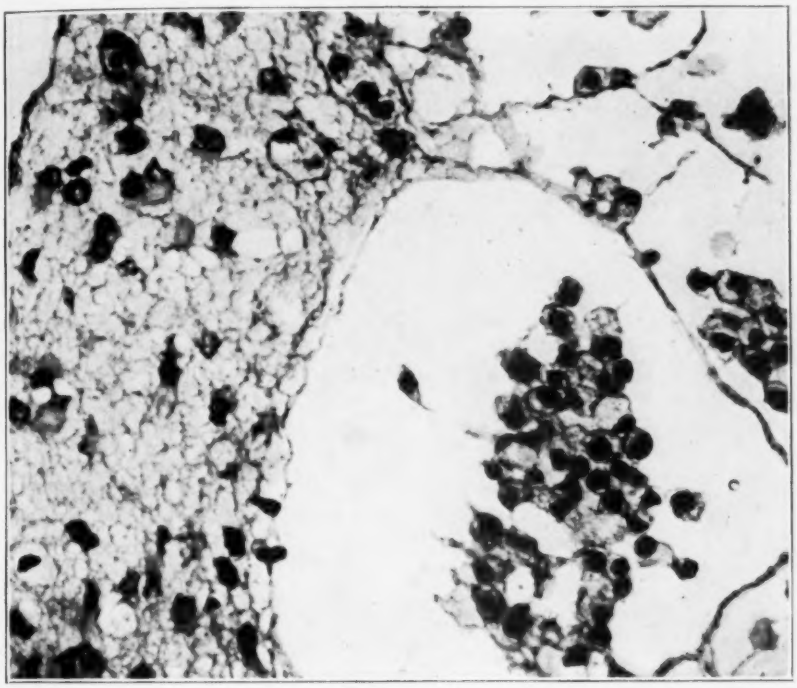

Fig. 4.—Section through spongy areas, showing accumulation of gitter cells within areas of liquefaction necrosis and glial proliferation with gemästete glia cells in the white matter. Hematoxylin and eosin; × 532.

degenerated with formation of fairly large cystic cavities, traversed by strands of trabeculae (fig. 1 *A*). The foramens of Monro were large, and the lateral and third ventricles were considerably dilated. The subcortical ganglia cut with increased resistance, and their structure could not be differentiated. The choroid plexus in the left lateral ventricle was enlarged and hemorrhagic and filled the dilated temporal horn. Section through the occipital lobes showed a large cystic cavity in the left lobe and enlarged hemorrhagic choroid plexuses filling the dilated occipital horns of the lateral ventricles (fig. 1 *B*).

Microscopic Examination of Brain.—The myelin sheath stains showed complete demyelination and liquefaction necrosis of the white matter of the cerebral hemispheres in a uniform, symmetric fashion. As a result the hemispheres presented a cystic, spongelike appearance (fig. 2*A*). The optic tracts stained well. The internal capsules were devoid of myelin. A few beaded and swollen myelinated

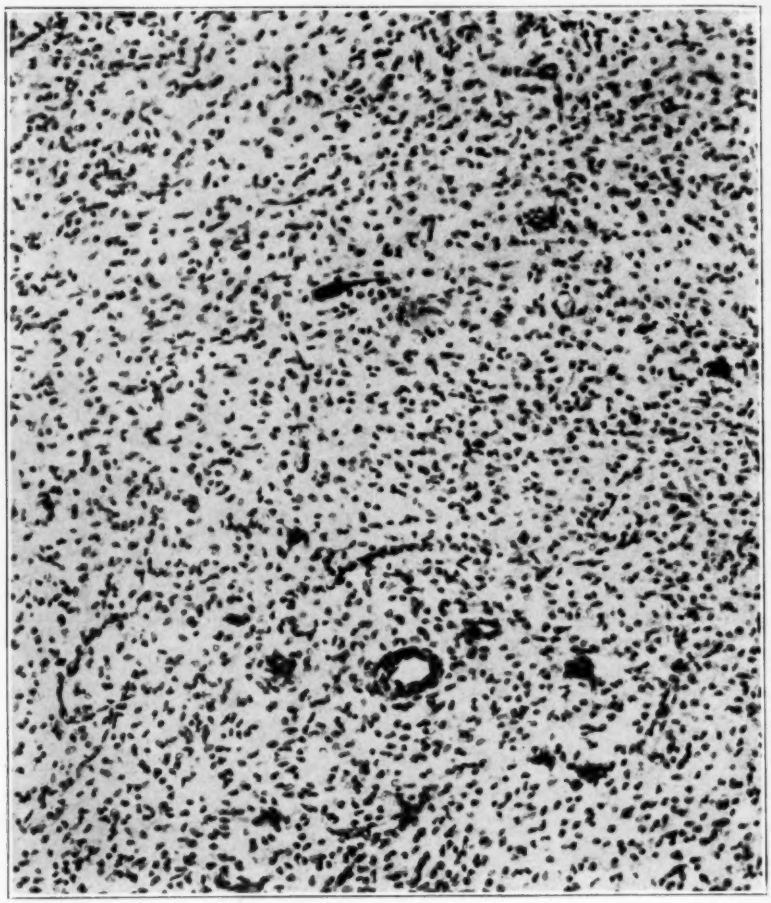

Fig. 5.—Section through the basal ganglia, showing paucity of ganglion cells and intense gliosis, composed mainly of astrocytes and microglia. Toluidine blue; × 160.

fibers were present in the external geniculate bodies and the peduncles. The cerebellum suffered less than the cerebrum, but several areas showed complete demyelination (fig. 2*B*). Within the brain stem the pyramidal tracts were not myelinated. The only myelinated tracts were the lemniscus medialis, the lemniscus lateralis, the fasciculus longitudinalis dorsalis and the pedunculus cerebellaris

superioris in the pons. In the medulla only the fasciculus longitudinalis dorsalis, the pedunculus cerebellaris inferioris and the lemniscus medialis showed myelination.

The pia-arachnoid was greatly distended over both hemispheres, and the subarachnoid space was filled with varying amounts of a cellular exudate composed of large monocytes, immature granulocytes, endothelioid cells and numerous phago-

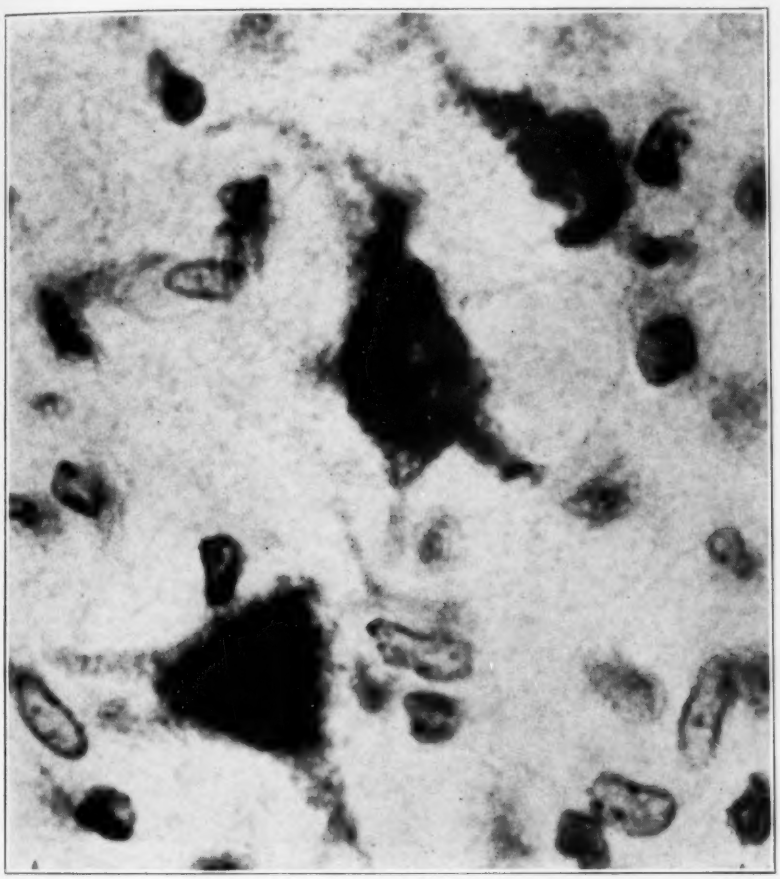

Fig. 6.—Calcified ganglion cells in the medial nucleus of the thalamus. Toluidine blue; × 1,700.

cytes containing blood pigment and fat. Only an occasional lymphocyte was encountered. Interspersed in the cellular exudate appeared many clumps of short and long chain streptococci. In places considerable free blood filled the subarachnoid space. There was comparatively little exudate at the base of the brain.

The cortex was for the most part a thin shell, without normal cytoarchitectural arrangement (fig. 3). There was an intense glial proliferation composed mainly

of astrocytes and microglia cells, the latter showing stages of transition to gitter cells. The astrocytes occurred freely as gemästete glia cells. There was marginal gliosis. The ganglion cells uniformly showed advanced, severe cell disease. An occasional calcified motor cell could be seen. The capillaries in the cortex showed hypertrophied endothelial nuclei. At the corticosubcortical margin, where the cystic cavities appeared, numerous gitter cells were arranged in rows and extended irregularly in finger-like projections into the cystic areas, which probably had been filled with gitter cells and products of liquefaction necrosis (fig. 4). The subcortical ganglia contained few ganglion cells and were densely packed with glia

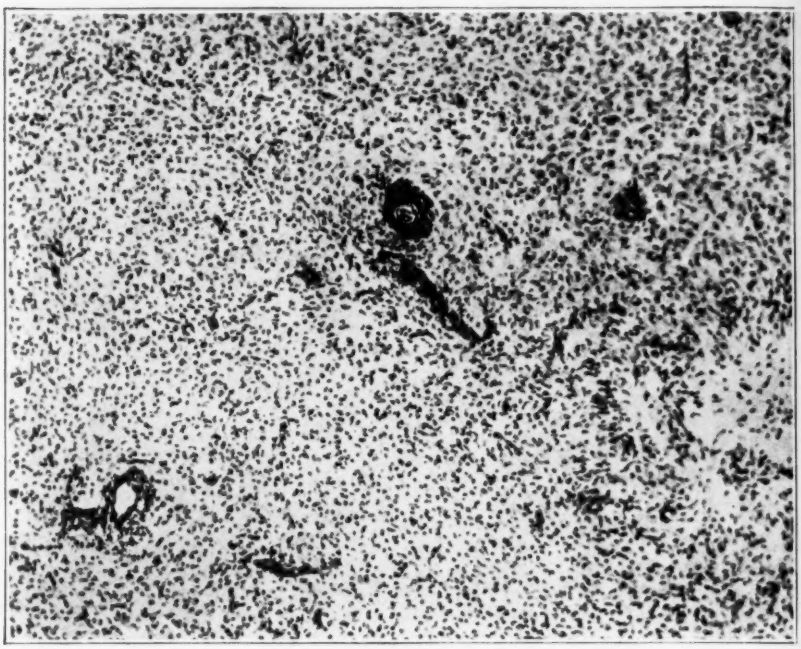

Fig. 7.—Section through the basal ganglia, showing pseudoinflammatory reaction. Note the perivascular cuffing and intense glial reaction with beginning liquefaction necrosis on the right. Toluidine blue; × 120.

(fig. 5). Astrocytes and microglia cells made up the glial proliferation. Several necrotic areas were observed in the basal ganglia. A few large ganglion cells were seen in the putamen, but these showed severe cell disease. Some of the ganglion cells in the medial nucleus of the thalamus had undergone calcification (fig. 6); others showed severe cell disease similar to that in the cortex. Several areas in the subcortical ganglia, notably in the pallidum and the region of the red nucleus, presented a pseudoinflammatory appearance (fig. 7). Considerable amorphous calcium was seen in the basal ganglia, occurring free both in the tissue and in the perivascular spaces. This was verified with the Kossa stain. Some

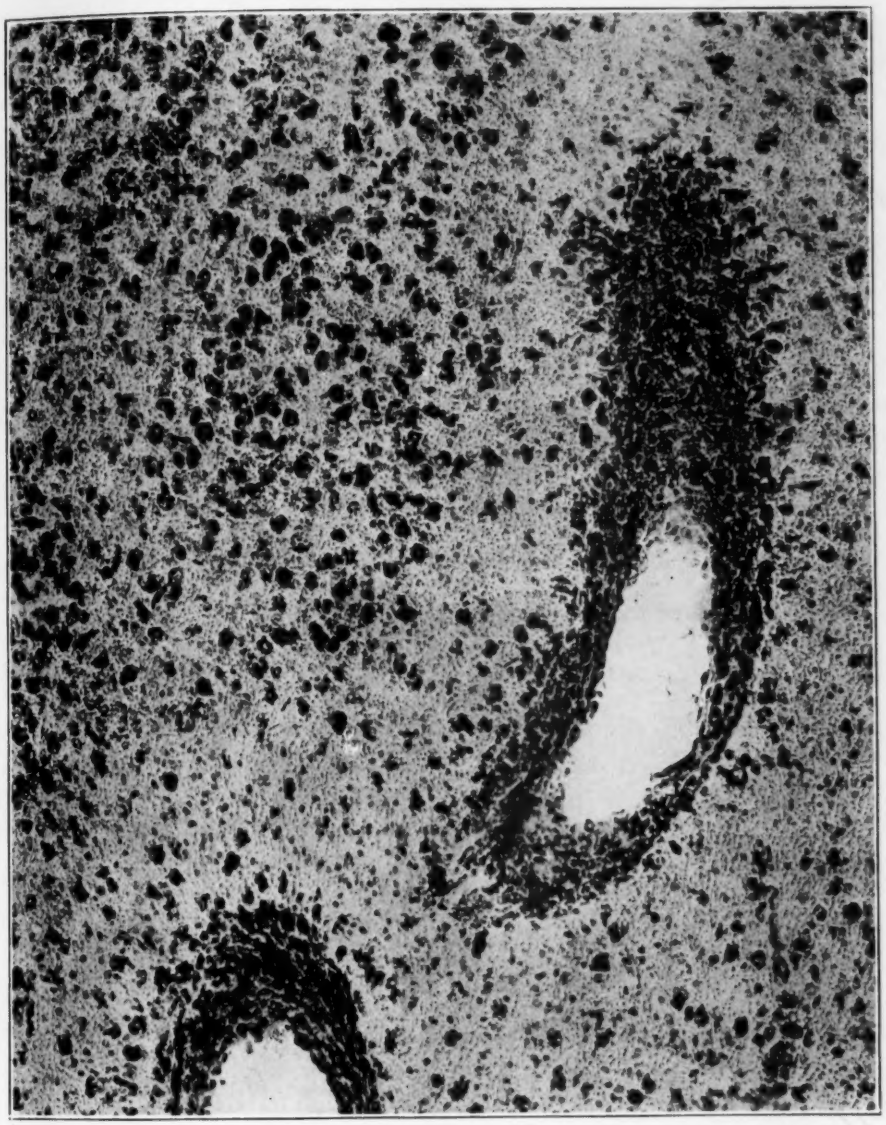

Fig. 8.—Fat stain, showing fat-laden gitter cells within the tissue and perivascular spaces. There is considerable free fat in the tissues. Herxheimer stain; × 160.

of the vessels were heavily cuffed with small, deeply staining nuclei, which the Herxheimer stain proved to be fat-laden gitter cells (fig. 8). The white matter of the cerebellum also showed intense gliosis, but not as pronounced as that in the cerebrum. The cerebellum did not show extensive cyst formation. Only an occasional lacuna was seen in the granular layer. The Purkinje cells showed

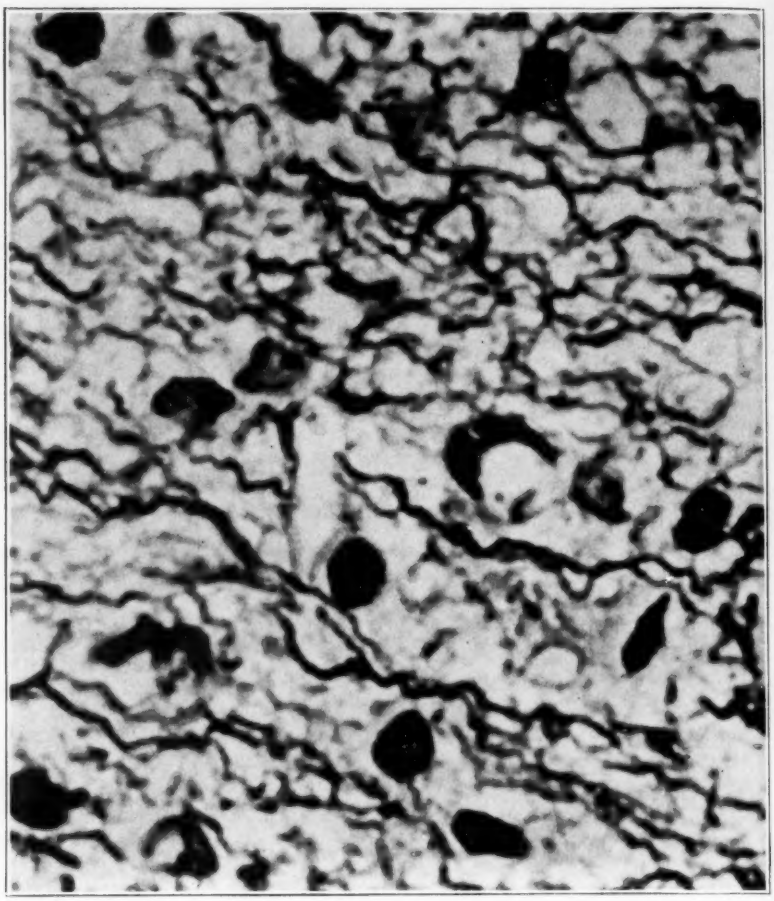

Fig. 9.—Tortuosity and swelling of axis-cylinders. Bodian stain; × 1,700.

swelling and homogenization. Others exhibited pyknosis. There were empty spaces corresponding to destroyed Purkinje cells.

The best preserved nerve cells were found in the pons, constituting the nuclear cells of the cranial nerves. Those in the ventral cochlear nuclei, however, showed vacuolation and other evidence of severe cell disease. The inferior olives contained few preserved cells.

The scarlet red stain of the cortex showed an enormous amount of fat, mainly within gitter cells but occasionally free in the tissue. The upper three layers of the cortex bore the brunt of this involvement. The fourth, or internal granular, layer was relatively free of fat. The infragranular layers also contained a considerable quantity of fat-laden gitter cells. In the small, spongelike lacunas were numerous gitter cells puffed out with fat. The subcortical ganglia were intensely and diffusely filled with fat-laden gitter cells (fig. 8). The perivascular spaces

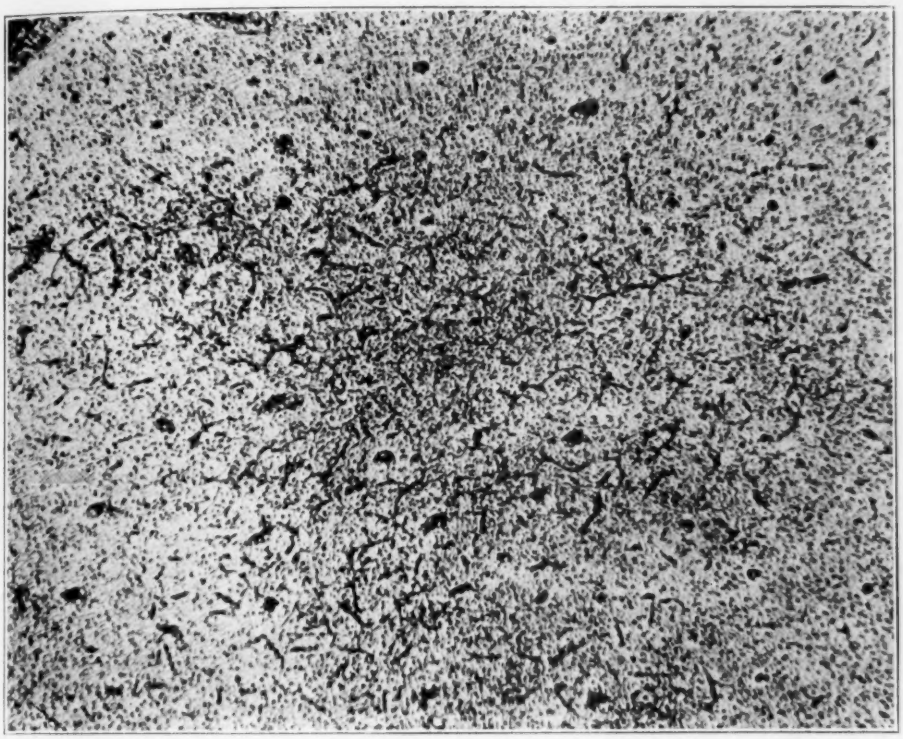

Fig. 10.—Scar in the temporal lobe, composed of increased capillary elements and fibroconnective tissue. Klarfeld stain; × 120.

were filled with gitter cells and free fat. Hemosiderin was not observed in the perivascular spaces.

The phosphotungstic acid hematoxylin stain showed a layer of glia fibers at the corticosubcortical margin, bordering the cystlike cavities. There were areas of gliosis adjacent to the ventricles.

The Bodian stain showed tortuosity and swelling of the axis-cylinders (fig. 9).

The Klarfeld stain revealed throughout the cerebrum occasional scars composed of newly formed vessels and fibroconnective tissue (fig. 10). The Cajal and

Hortega stains revealed that the glial proliferation consisted mainly of astrocytes and microglial cells. The microglia cells were in various stages of transition into gitter cells (fig. 11).

Microscopic examination of the enlarged and hemorrhagic choroid plexus revealed large blood sinusoids lined by a single layer of endothelial cells. Many of the choroid villi showed dilatation.

The large vessels at the base of the brain were normal. The capillaries throughout exhibited endothelial thickening.

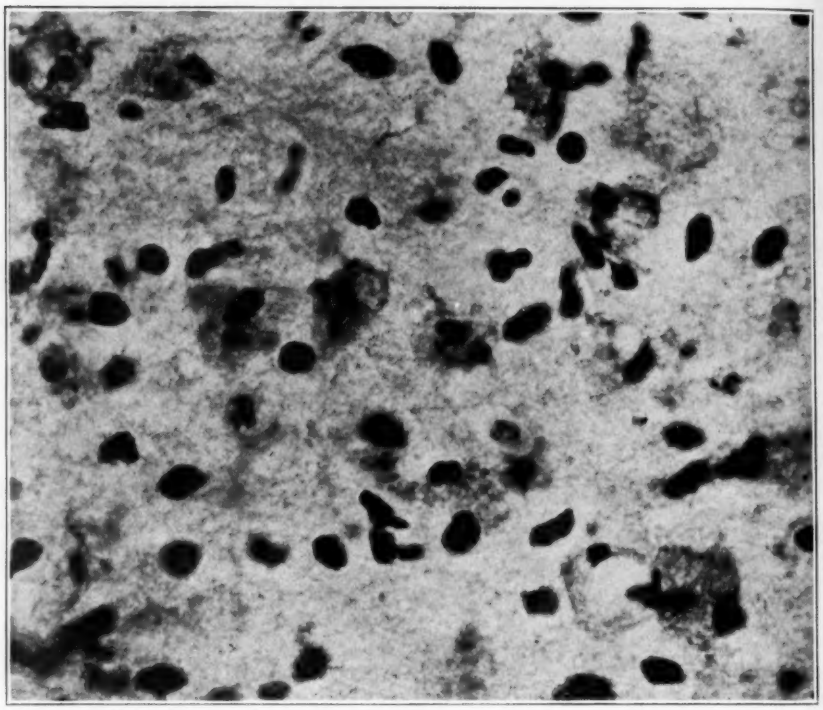

Fig. 11.—Microglial proliferation, showing transition forms to compound granular corpuscles. Hortega silver carbonate stain; × 650.

COMMENT

In view of the close similarity, clinically and pathologically, between "swayback" in lambs and the condition described in this presentation, we believe that it is important to review briefly the condition known as "swayback." It is possible that some hint might be obtained from the study of cases of "swayback" which will help in understanding the as yet incomplete story of the demyelinating diseases in man. We, therefore,

propose to compare the syndrome in our case with "swayback" and to show the relation to Schilder's disease in man.

Clinical Phase.—1. "Swayback" occurs in the offspring of normal ewes and is present in most instances from birth. It is characterized by generalized incoordination and marked spasticity, making it difficult or impossible for the animal to walk. In some animals blindness occurs. Tremors are inconstant; convulsions do not occur. The course is usually downward, without remission, to death. There is generally no fever during the course of the disease. The fatal termination is usually hastened by bronchopneumonia, meningitis or marasmus.

2. In the case described in this paper the patient was the offspring of normal, non-Jewish parents. Labor had been prolonged, and the child showed marked asphyxia. The clinical condition was present at birth and was manifested by spasticity of the limbs, which gradually increased. There were occasional convulsive seizures, difficulty in swallowing and marasmus, and the child died within twelve weeks. Necropsy showed bronchopneumonia, terminal meningitis and marasmus.

3. Schilder's disease is usually described as a nonfamilial condition, manifesting itself frequently in early life and showing disturbance of vision as the result of subcortical destruction in the occipital lobe. There is usually gradual progression of symptoms as the result of the rostral march of the disease, with sensory, motor and frontal lobe signs and symptoms. The course is progressive, with occasional convulsive seizures and most often without fever.

Pathologic Phase.—1. In "swayback" of lambs macroscopic examination of the brain usually shows the following changes (Innes and Shearer [1]): internal and external hydrocephalus, atrophy of the brain, aplasia of the cerebral convolutions, liquefaction and gross cavitation of the white matter of diffuse and symmetric distribution, with a thin shell of cerebral cortex that appears relatively well preserved. The basal nuclei usually appear normal.

The microscopic appearance is characterized by the constant presence of demyelination of the hemispheric white matter and secondary involvement of the axis-cylinders, with spongy, porous areas and cavitation within the white substance, and fat deposition. In the cortex severe ganglion cell disease is universal; glial proliferation is mainly astrocytic, and microglial changes are minimal, with the oligodendroglia not participating in the process.

2. In our case the important gross observations were internal and external hydrocephalus, cortical atrophy with microgyria, gross symmetric subcortical cystic degeneration and increased density of the subcortical nuclei.

The microscopic examination in our case showed complete diffuse demyelination of the hemispheric white matter, with symmetric cavitation as the result of liquefaction necrosis, and incomplete demyelination of the cerebellar white matter. The spongy subcortical tissue contained numerous fat-laden gitter cells. An astrocytic increase was present, with both progressive and regressive changes. The axis-cylinders were sparse, tortuous and swollen.

The normal architectural arrangement of the cerebral cortex was greatly disturbed as the result of decrease in ganglion cells and increase of astrocytic glia. Many fat-laden phagocytic cells were present. Those ganglion cells that were mature showed severe cell disease and occasional calcification; for the most part, however, the ganglion cells were immature.

Within the subcortical ganglia severe gliosis with marked accumulation of gitter cells was seen. Here the ganglion cells were also sparse, and degenerative changes were present in those remaining. Some showed calcification, and calcium was noted free in the tissues.

3. In cases of Schilder's disease of the chronic type the gross examination usually reveals a shrunken brain. On sectioning the hemispheric white matter is seen to be grayish, gelatinous and spongy. Cavitation may occur. The ventricles are usually widened, and the arcuate, or U, fibers stand out prominently, being often appreciably raised above the level of the damaged tissues. The gray matter usually appears normal to gross inspection.

Microscopic examination in cases of Schilder's disease reveals wholesale demyelination of the affected regions. The U bundles are usually spared, but they also may be attacked. The cortex is preserved in the early stages, but later parenchymatous degeneration of a widespread character can be seen. Glial changes are pronounced and at times characteristic. An astrocytic network is frequently present, leading at times to degenerative manifestations, including the gemästete glia cells of Nissl. Fat-laden phagocytes are present in great numbers and most often are densest around the vessels, giving the impression of an inflammatory reaction.

The extreme degree of demyelination of the cerebral hemispheres and, to a much lesser extent, of the cerebellum raises the problem as to the nature of the underlying process. The question concerning possible inhibition or aplasia of myelin formation, as discussed by Russell and Tallerman [11] and by Innes and Shearer,[1] can be answered in our case by

11. Russell, D. A., and Tallerman, K. H.: Familial Progressive Diffuse Cerebral Sclerosis of Infants, Arch. Dis. Childhood **12**:71, 1937.

stating that the pathologic changes point to an active degenerative process. This is indicated by the almost complete loss of subcortical myelin, occurring even in those areas which prior to birth should be myelinated, as demonstrated by His,[12] Flechsig[13] and Keene and Hewer.[14] That myelin had been present is indicated by the large quantities of fat found in the cortex, as well as in the subcortex. The activity of the degeneration is further attested to by the large degenerative cystic areas and the smaller spongelike, porous areas and by the acute and chronic severe cell disease involving the ganglion cells both of the cortex and of the subcortical nuclei.

Apparently, little can be gained thus far from an investigation of the antecedents in cases of "swayback," Schilder's disease and related disorders. The parents of the patient reported here were normal, nonconsanguineous persons, and their mode of living and dietary habits were in no way abnormal.

That "swayback" is not of bacterial or virus origin has been demonstrated by Stewart,[15] Bennetts[16] and Innes and Shearer.[1] In their excellent article Innes and Shearer discussed at length the possible etiologic aspects of "swayback" and concluded, in addition, that no evidence of a hereditary or a developmental factor exists, that lead poisoning may in some way be concerned in the origin of the condition, that a disturbance in copper metabolism in pregnant ewes may play an important etiologic role and that the toxic agent, whatever its nature, "causes no obvious disturbance in the health of the ewe but exerts a pathogenic effect on the foetus or young lamb." No evidence of an inflammatory process can be demonstrated in "swayback." In our case, likewise, no changes other than the purulent meningitis, which was terminal, were present which could be said to be the result of inflammation. The origin of the degeneration appeared to be toxic. Although Schilder's[3] original designation of the disease bearing his name was encephalitis periaxialis diffusa, most authors agree that Schilder's disease is not an inflammatory but a degenerative process due to some undetermined toxic agent.

Innes and Shearer[1] established clearly that "swayback" of lambs begins in utero. This is a significant observation, especially since the

12. His, W., cited by Keibel, F., and Mall, F. P.: Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 106.

13. Flechsig, P.: Anatomie des menschlichen Gehirns und Rückenmarks auf myelogenetischer Grundlage, Leipzig, Georg Thieme, 1920, vol. 1.

14. Keene, M. F. L., and Hewer, E. E.: Some Observations of Myelination in the Human Central Nervous System, J. Anat. **66**:1, 1931.

15. Stewart, W. L.: Swingback (Ataxia in Lambs), Vet. J. **88**:133, 1932.

16. Bennetts, H. W.: Enzootic Ataxia of Lambs in Western Australia, Australian Vet. J. **8**:137 and 183, 1932.

evidence, both clinical and pathologic, in our case points to the likelihood that the process was also present at the time of birth. It is noteworthy that the birth in our case was delayed and resuscitation difficult. It not infrequently happens that dystocia and severe asphyxia of the newborn are found to occur in children who eventually show signs and symptoms that are attributed to birth trauma (Collier [17]; Heyman [18]).

It is probable that many cases similar to ours have been buried in the literature under titles that give no indication of the nature of the process. Among these can be included the case described by Brocher [19] under the name *polyporencephalie*. In this report the clinical and pathologic picture showed a remarkable resemblance to that in "swayback" in lambs and to the condition in our case. Brocher's title is misleading in that he himself stated that "nowhere was there a communication of these spaces with the lateral ventricles." Still another case of a human disorder which bears a close resemblance to "swayback" is one in a group reported by Hallervorden [20] under the descriptive title of "vascular disturbances in the etiology of congenital mental deficiency." The gross appearance of the brain in this case was similar to that in our case and to that seen in cases of "swayback." Unfortunately, Hallervorden's case was inadequately described clinically and pathologically, but he concluded that "the etiology remains obscure."

We can state, in passing, that the occurrence of cases similar to the one we report may alter conceptions of antenatal processes and of birth trauma. We need mention only the cerebral diplegia in infants delivered by cesarean section [21] or the familial form of diplegia reported by Jakob and Scaravelli [22] in eight members of one family.

SUMMARY AND CONCLUSIONS

1. In an infant born partially asphyxiated after a prolonged labor there developed progressive spastic diplegia, occasional convulsive seizures and marasmus. Death occurred within twelve weeks of pneu-

17. Collier, J.: The Pathogenesis of Cerebral Diplegia, Brain **47**:1, 1924.

18. Heyman, C. H.: Infantile Cerebral Palsy (Spastic Paralysis): Discussion on Etiology, J. A. M. A. **111**:493 (Aug. 6) 1938.

19. Brocher, J. E. W.: Polyporencephalie, Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:107, 1932.

20. Hallervorden, J.: Kreislaufstörungen in der Aetiologie der angeborenen Schwachsinns, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:527, 1939.

21. Patten, C. A.: Cerebral Birth Conditions, with Special Reference to Cerebral Diplegia, Arch. Neurol. & Psychiat. **25**:453 (March) 1931.

22. Jakob, C., and Scaravelli, A.: A propósito de un caso de ocho hermanos con idiocia, sordomudez y cuadriplejía espasmódica familiar, Rev. neurol. de Buenos Aires **5**:283, 1940.

monia and purulent meningitis. The brain showed maldevelopment, subcortical demyelination, liquefaction necrosis with cyst formation and underdevelopment and degeneration of the cortex.

2. The clinical and pathologic aspects of the condition in this case resemble in most details those of "swayback" in lambs.

3. In view of the fact that "swayback" has been shown to develop in utero and that in our case comparable signs and symptoms were apparent at the time of birth, the conclusion is justified that in our case the condition was of antenatal origin.

4. The features in this case may help to strengthen further the viewpoint of those who believe that antenatal factors may explain some of the clinical syndromes often attributed to birth trauma.

COMPARATIVE VALUE OF SOLANACEOUS ALKALOIDS IN TREATMENT OF PARKINSON'S SYNDROME

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NEW YORK

PHARMACOLOGIC ASPECTS

It is generally accepted that solanaceous alkaloids are effective in the symptomatic treatment of Parkinson's syndrome but that none of them is entirely satisfactory. There is no agreement, however, as to the comparative value of the individual alkaloids and their combinations. The well known suggestibility of patients with this syndrome renders such comparative studies difficult and has actually misled many investigators.

Nevertheless, most clinicians admit the superiority of Roemer's[1] treatment with massive doses of atropine and of the so-called Bulgarian treatment.[2] Different as the two therapeutic methods are qualitatively, they have in common the same quantitative principle: the use of large doses approaching the limit of toxicity. After Bremer's[3] observation that an unusually high tolerance to atropine exists in cases of chronic encephalitis, Roemer[1] concluded that massive doses are required for patients with this disease. His therapeutic experiments were highly successful and his results generally confirmed. On the other hand, Ivan Raeff, who originated the Bulgarian treatment, unconsciously acted on the same principle of the massive dose. He empirically administered decoctions of belladonna root in amounts which caused "crises" exhibiting all the characteristics of atropine intoxication. By decreasing these doses below the threshold of toxicity he obtained good results, subsequently confirmed by a great number of investigators. This quantitative aspect of the therapeutic problem cannot be overemphasized. Any treatment with belladonna alkaloids seems to be unsatisfactory unless doses are given which produce definite side effects but avoid more serious toxic manifestations.

1. Roemer, C.: Zur Atropinbehandlung der enzephalitischen Folgezustände, München. med. Wchnschr. **77**:2156, 1930; Die Atropinbehandlung der enzephalitischen Folgezustände, Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:724, 1931; Zur Therapie der enzephalitischen Folgezustände, Med. Klin. **28**:224, 1932.

2. Vollmer, H.: The Bulgarian Treatment of Postencephalitic Parkinsonism, J. Mt. Sinai Hosp. **6**:93, 1939.

3. Bremer, F. W.: Ueber die Unterempfindlichkeit gegenüber Atropin bei den chronisch-amyostatischen Encephalitis-Kranken, Arch. f. klin. Med. **149**:340, 1925.

Individual belladonna alkaloids and their combinations have similar side effects, but their therapeutic index, i. e., the relation between the toxic and the therapeutic effect, varies widely. Daily doses of from 15 to 120 mg. of atropine, as advocated by Roemer,[1] bring about less clinical improvement and more toxic symptoms than from 1.25 to 10.5 mg. of a combination of hyoscyamine, atropine and scopolamine which I [4] have used. Obviously, preparations with a higher therapeutic index are preferable.

In addition to these quantitative aspects, qualitative principles are to be taken into consideration. If the Parkinson syndrome may be regarded as an entity, the therapeutic values of the three main alkaloids must differ as a result of their different pharmacologic actions.

	Effect	
	Central Nervous System	Vagus Nerve
Atropine	Stimulating	Paralyzing
Hyoscyamine	Less stimulating	More paralyzing
Scopolamine	Paralyzing	Paralyzing

The peripheral vagotonic symptoms of parkinsonism may be controlled by each of the three alkaloids, since they all have a similar action on the vagus nerve. They differ in their effects on the central nervous system. With regard to the symptoms of parkinsonism referable to the central nervous system, an ideal drug should control mental depression, difficulty in initiating movements, muscle rigidity and tremor but should avoid overstimulation, resulting in excitement and hallucinations. Though there is no evidence that the central nervous system is depressed in chronic encephalitis, practical experience seems to indicate that stimulating drugs are therapeutically more effective than depressants. Sedatives do not benefit patients with this disorder, and, of the belladonna alkaloids, the stimulating atropine appears to achieve better results than the paralyzing scopolamine. Since the pattern of action of the various alkaloids on the central nervous system as well as the pattern of central nervous disturbance in parkinsonism is not completely understood, one must rely on empiric facts rather than on theoretic considerations. From the clinical point of view, however, none of the individual belladonna alkaloids proves to be ideal.

Atropine sulfate in doses of from 15 to 120 mg. brings about satisfactory and definitely better results than the traditional smaller doses. However, disturbing toxic effects regularly accompany this improvement. The resulting mydriasis is continuous and must be corrected by glasses. Excitement and hallucinations frequently occur. The

4. Vollmer, H.: "Bulgarian Treatment" of Parkinson's Disease: Pharmacologic Aspects and Clinical Effects of Alkaloids of Belladonna Root, Arch. Neurol. & Psychiat. **43**:1057 (June) 1940.

suppression of the salivary and gastrointestinal secretions causes not only disturbing dryness of the throat and complete anorexia but more serious results. Attention is called to the alarming reports of Siegmund [5] and Fehsenmeier.[6] They found that prolonged treatment, even with smaller doses of atropine, may result in severe, or even fatal, disturbance of tonus, motility and secretion of the gastrointestinal tract. Postmortem examination in 6 cases revealed the formation of megasigmoid or megacolon, with ulcerations or ileus and acute dilatation of the stomach. These observations should be taken as a warning.

Scopolamine brings about sedation of the central nervous system, particularly of the motor centers. In some cases of parkinsonism with mental excitement and motor restlessness it might be the drug of choice. In the majority of other cases it relaxes to a slight extent the muscle rigidity but, on the other hand, further impairs the initiation of movements and increases the mental depression. It usually does not benefit the motor power of the patient. Contradictory statements of the patients may be due to the sedative effect of scopolamine. The patients feel, rather than are, better after this medication. Subjective improvement is usually reported by the patient only at the beginning of scopolamine therapy. The therapeutic index of scopolamine hydrobromide seems to be low. Daily doses of from 0.65 to 1.95 mg. usually cause pronounced side effects, in many cases without materially benefiting the neurologic condition. Some patients report a sensation of being "drunk" or "dazed." Larger doses are a definite danger to the respiratory and circulatory centers.

Studies on the effect of hyoscyamine, the levorotatory isomer of atropine, are lacking. Perhaps this drug has not been used because it is unstable in dilution and is partly changed to atropine during extraction (Cushny,[7] Sollmann [8]). Many theoretic considerations are in its favor. It is less depressing on the central nervous system than scopolamine and less stimulating than atropine, thus avoiding the disadvantages of scopolamine as well as of atropine. However, it is twice as effective as atropine in paralyzing the parasympathetic nerve endings, which might cause disturbing side effects. My own experience in 14 cases

5. Siegmund, H.: Anatomisch nachgewiesene Folgen von Tonus- und Motilitätsstörungen des Verdauungskanals bei Enzephalitikern, die mit Atropin behandelt wurden, München. med. Wchnschr. **82**:453, 1935.

6. Fehsenmeier, H.: Klinische Untersuchungen über das Verhalten des Magen-Darmkanals bei mit Atropin behandelten Enzephalitikern, München. med. Wchnschr. **82**:1723, 1935.

7. Cushny, A. R.: Pharmacology and Therapeutics, ed. 12, Philadelphia, Lea & Febiger, 1940, p. 502.

8. Sollmann, T.: Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 359.

seems to indicate that hyoscyamine is superior to atropine as well as to scopolamine alone but is inferior to a combination of all three alkaloids in a certain ratio.

The use of alkaloid combinations is not new. All extracts of Atropa belladonna, Hyoscyamus niger and Datura stramonium contain a combination chiefly of atropine, hyoscyamine and scopolamine. Only the extracts from Datura stramonium and from the roots of Atropa belladonna have been widely used in the treatment of Parkinson's syndrome. In the beginning these extracts were accepted enthusiastically. Stramonium, after an experience of decades, has lost a good deal of its popularity. At present extracts of belladonna root are highly favored. They seem to be more effective than other preparations. However, the primary overenthusiasm, as expressed by Panegrossi,[9] is on the decline.

The superiority of extracts of belladonna root has been ascribed [4] to a favorable combination of the known belladonna alkaloids rather than to any additional substance not yet determined. Whatever may account for their special effect, one principal objection is to be raised against all crude extracts. As pharmacologic principles are now conceived, their use would be a retrogression. They contain, instead of pure substances in known proportions, a variety of alkaloids in ever changing proportions, depending on the age of the plant, harvest time, climate, geographic location, degree of cultivation and other factors. Consequently, their pharmacologic action is not uniform and their therapeutic effect is not dependable or predictable. Toxic reactions may occur. This state of affairs cannot be remedied by standardization of such extracts as to their total alkaloid content.

All investigations on Datura stramonium, particularly those of Sievers,[10] Chopra [11] and Langenhan,[12] impress one not only with the wide variations of the total alkaloid content in various specimens of this plant but with the entirely different proportions of the individual alkaloids found in different specimens. By analogy, the same variability may be anticipated for belladonna roots. In addition to these original

9. Panegrossi, G.: Sulla così detta "cura bulgara" del parkinsonismo postencefalitico; Sulle recenti acquisizioni nella cura del parkinsonismo encefalitico, Policlinico (sez. prat.) **42**:56, 506 and 1487, 1935; Sopra un nuovo metodo di cura dell' encefalite epidemica cronica a forma parkinsoniana, Riv. osp. **27**:3, 1937; Ueber die neue Heilmethode der chronischen epidemischen Enzephalitis mit Parkinson-Erscheinungen, Deutsche med. Wchnschr. **64**:669, 1938.

10. Sievers, A. F.: Distribution of Alkaloids in the Belladonna Plant, Am. J. Pharm. **86**:97, 1914; The Possibility of Improving the Commercial Belladonna Crop Through Selection, J. Infect. Dis. **88**:193, 1916.

11. Chopra, R. N.: Indigenous Drugs of India: Their Medical and Economic Aspects, Calcutta, Art Press, 1933, p. 128.

12. Langenhan, H. A.: The Alkaloidal Content of Stramonium Leaves, Bulletin 692, Madison, University of Wisconsin Press, 1914, science ser., vol. 4, no. 6.

variations, extracts are not stable, whatever solvent and method of extraction may be used. Belladonna alkaloids are esters and as such are extremely delicate. A labile equilibrium exists between the levorotatory and the racemic form of the alkaloids,[13] resulting necessarily in varying pharmacologic action. No doubt a drug so characterized does not meet pharmaceutic standards, and its clinical use is not without risk.

CLINICAL EVALUATION

Empirically, a combination of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide [4] proved to be effective against the Parkinson syndrome. As was outlined in a previous publication,[4] this synthetic compound has been found at least equivalent to the most effective natural extracts from Bulgarian or other belladonna roots, and its therapeutic effect has been ascribed to a pharmacodynamic synergism of the three alkaloids.

There remained the problem of determining the comparative values of this alkaloid compound, single alkaloids, natural extracts, such as stramonium, and other synthetic compounds with a different ratio of alkaloids. In order to obtain as objective an evaluation as possible, every new drug or composition was offered to the patient without suggestion of any kind. The patient was asked as a favor to try "something else," to continue taking it if he found it more effective but to discontinue it as soon as he found his condition getting worse. Objective as well as subjective evaluation was aimed at. If suggestion was avoided, the two usually agreed. Suggestive influences resulted in disagreement between subjective statements and objective findings. In such an event, the comparative evaluation was repeated.

The aforementioned compound, consisting of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide, hereafter designated as belladonna alkaloid compound RT,[14] was first compared with the single alkaloids.

Comparative Value of Single Alkaloids and Belladonna Alkaloid Compound RT.—Atropine: Of 9 patients who had been taking atropine for longer periods, 1 became worse, 1 had to discontinue treatment because of paralysis of accommodation, 5 were not improved and 2 were slightly or temporarily improved. All 9 patients were improved by subsequent treatment with smaller doses of belladonna alkaloid compound RT, 8 of them decidedly. Muscle rigidity, tremor and general spirits were most benefited. A more detailed analysis of a single case illustrates this.

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13. Cushny.[7] Sollmann.[8]

14. Purchasable as rabellon from Sharp & Dohme, Philadelphia. This compound was designated as compound T in the previous publication.[4]

S. G., a 52 year old concert singer, had not been able to work for the past ten weeks because of gradually increasing symptoms of parkinsonism. He was first treated with atropine and subsequently with smaller amounts of belladonna alkaloid compound H, with the following results. On March 31, 1939 the patient was symptom free, started to work, could play the piano and went on a concert tour.

Treatment	Atropine Sulfate, 0.5 % Solution, 8 Drops Three Times a Day	Atropine Sulfate, 0.5 % Solution, 9 Drops Three Times a Day	Belladonna Alkaloid Compound H, 0.3 % Solution, 5 Drops Three Times a Day *
Date	3/3/1939	3/8/1939	3/31/1939
Symptoms			
General spirits	Weak; depressed	"Very bad"	"Much better"
Associated movements	—		++
Tremor right hand	—		—
Tremor left hand	+		—
Tremor right foot	—		—
Tremor left foot	++		—
Rigidity	++		—
Toxic Symptoms			
Dry throat	+	+	—
Dizziness		+	—
Hallucinations		+	—
Nausea		+	—
Vomiting		+	—

*Five drops of the aqueous-alcoholic preparation of the synthetic belladonna alkaloid compound H is equivalent to 1 tablet of compound RT, which has an identical composition.

Scopolamine: A comparison of the effects of scopolamine and compound RT was carried out on 21 patients. Of these patients, 1 became worse, 16 were not improved, 2 were temporarily improved and 2 were slightly relieved under scopolamine treatment. All 21 patients were improved even with smaller doses of compound RT, 12 of them notably; several patients could take up their former occupation. Rigidity, tremor and depressive states were particularly benefited, and the side effects were not increased. The following case demonstrates the difference in the results with the two drugs.

M. S., a man aged 54, had been suffering from severe parkinsonism for seven years. For the past five years he had been taking 5.0 mg. of scopolamine hydrobromide a day. In spite of this medication, severe parkinsonian symptoms were present: sialorrhea, hyperhidrosis, restlessness, depression, marked tremor and rigidity of all extremities, loss of associated movements, masked facies, slow gait and retropulsion; the patient could not write, button his suit or wind his watch and frequently could not eat without assistance. Within twenty days scopolamine

was gradually replaced by smaller doses of belladonna alkaloid compound RT, 4.0 mg. per day. According to the patient's own statement, he felt "50 to 75 per cent better." He could eat, write, button his suit and wind his watch without help; rigidity, muscle pain, hyperhidrosis, salivation and restlessness disappeared; tremor, gait and general spirits were noticeably improved. None of the toxic effects caused by scopolamine was present except for occasional slight dryness of his mouth. This improvement is well illustrated by samples of his handwriting (fig. 1). Another patient showed marked deterioration of his condition after compound RT was replaced by scopolamine, as demonstrated by samples of his handwriting shown in figure 2.

Hyoscyamine: Of special interest is the comparison of the effects of compound RT and hyoscyamine alone. Fourteen patients who previously had been taking belladonna alkaloid compound RT for from three

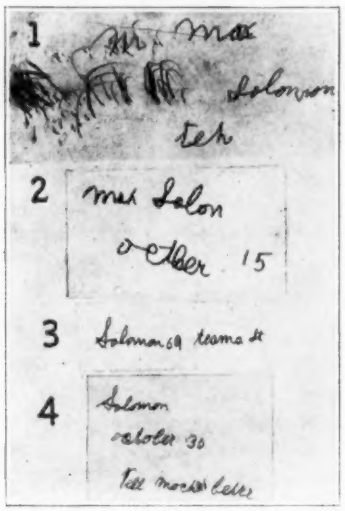

Fig. 1.—Handwriting of M. S., aged 54, with encephalitis, illustrating the superiority of smaller doses of compound RT over larger doses of scopolamine hydrobromide alone. *1* shows handwriting during treatment with 5.0 mg. of scopolamine hydrobromide; *2*, handwriting after five days of treatment with 2.5 mg. of belladonna alkaloid compound RT; *3*, handwriting after thirteen days of treatment with 3.5 mg. of compound RT, and *4*, handwriting after twenty days of treatment with compound RT.

to twenty-four months were given tablets of the same appearance but containing 0.5 mg. of hyocyamine hydrobromide. The patients were asked to take these tablets as long as they found them as effective as or superior to compound RT, but at least for four to seven days before making a statement or returning for reexamination. All patients were advised to take the same amount of the hyoscyamine tablets as they had been taking of compound RT up to this time. In the case of 14 patients

Fig. 2.—Handwriting of a patient with postencephalitic parkinsonism who had been unable to write his name (*1*) for seven years. He regained ability to write after treatment with belladonna alkaloid compound RT for one week. Sample *2* was obtained after six days' treatment (Nov. 11, 1938); sample *3*, after seven to ten days' treatment, and sample *4*, after nine months' treatment. His handwriting deteriorated materially after changing from compound RT to scopolamine (*5*, taken March 6, 1940).

hyoscyamine proved to be inferior to equal amounts of compound RT. Hyoscyamine was less effective and caused more side effects; several patients became more depressed and showed more rigidity and tremor. All patients preferred compound RT and returned to its use. Hyoscyamine in comparatively smaller doses diminished the side effects but also the therapeutic benefit. Generally, clinical improvement decreased with smaller doses.

None of the individual alkaloids proved to be equivalent to compound RT. Hyoscyamine seemed to be superior to atropine, as well as to scopolamine. However, its vagomimetic side effects were disturbing, and its beneficial effect on the neurologic symptoms did not equal those of compound RT.

Comparative Value of Stramonium and Compound RT.—The effect of stramonium was compared with the action of compound RT on 19 patients who had been taking stramonium from various sources for a considerable length of time. In spite of this treatment, all patients presented more or less pronounced symptoms. According to their own statements, 14 patients were not benefited and 5 were slightly or temporarily improved with stramonium. Subsequent treatment with compound RT relieved all 19 patients subjectively as well as objectively, 13 of them to a pronounced degree. Rigidity was decreased in 17 patients; tremor was relieved in 15 patients and muscle pain in 7; the general spirits of almost every patient improved, and symptomatic benefit was equivocal in only 2 patients. A graphic illustration of the superiority of belladonna alkaloid compound RT over larger doses of stramonium is shown in figure 3.

Comparative Value of Compound RT and Other Belladonna Alkaloid Compounds.—A great number of experiments previously reported [4] led me to believe that the range of greatest efficacy with the smallest possible dose is found with a combination of alkaloids in the following proportions: 75 to 95 per cent hyoscyamine hydrobromide, 5 to 15 per cent atropine sulfate and 1 to 5 per cent scopolamine hydrobromide. Even within these limits, compound RT proved to be more effective than other variations. It appeared conceivable that an increase of the proportion of scopolamine might increase the efficacy of the compound. Therefore, the results of administration of a mixture consisting of 75 parts hyoscyamine hydrobromide, 10 parts atropine sulfate and 15 parts scopolamine hydrobromide, designated as compound A, were compared with those of equal doses of compound RT in 23 cases of parkinsonism. Some of the patients neither felt nor showed any difference between the effects of the two preparations. In 16 of the 23 cases, however, compound A proved to be less effective and to cause more side effects. It might be anticipated that restless patients with parkinsonism would

respond to compound A, with its higher proportion of scopolamine, at least as well as to compound RT. However, the fact remains that the majority of the patients were more benefited by compound RT. Figure 4 shows the comparative effects of compound RT and compound A on the handwriting.

Finally, a comparative study was undertaken of compound RT and another mixture in which hyoscyamine was replaced by atropine. According to pharmacologic studies and clinical experiments, hyoscyamine appeared to be the most essential component of, though in itself not equivalent to, compound RT. The effects of compound RT were

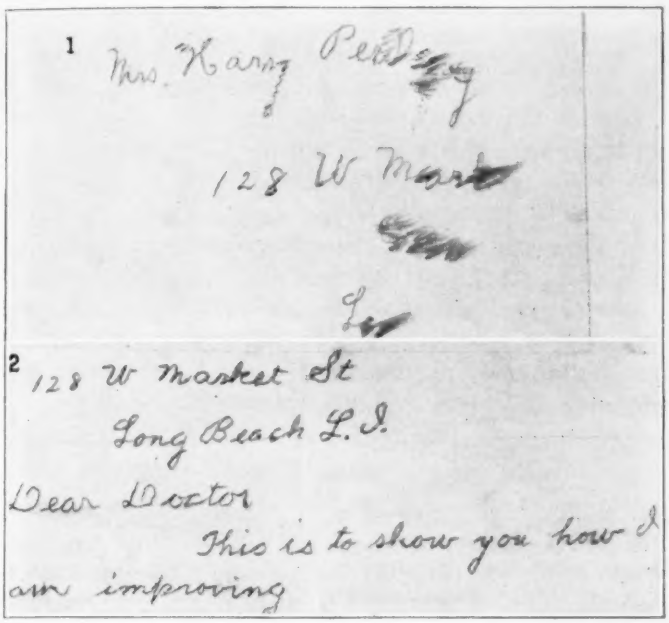

Fig. 3.—Handwriting of a patient with postencephalitic parkinsonism under treatment with stramonium (90 drops a day) (*1*). Note the influence of severe tremor, which makes writing almost impossible. After two weeks' treatment with smaller amounts of belladonna alkaloid compound RT (1¾ tablets, containing 0.8 mg. of total alkaloids, four times a day) the handwriting (*2*) was greatly improved.

compared with those of equal doses of compound Y, consisting of 94 per cent atropine sulfate and 6 per cent scopolamine hydrobromide, in 13 cases of postencephalitic parkinsonism. This atropine-scopolamine compound proved to be not only inferior to equal amounts of belladonna alkaloid compound RT but in many cases essentially ineffective. Most of the symptoms which had been present before any treatment and had

been greatly relieved with administration of compound RT recurred after compound RT had been replaced by compound Y. These results seem to indicate that hyoscyamine is the most important constituent of compound RT and that atropine is effective only in much higher doses than is compound RT.

Clinical Effects of Compound RT.—No serious untoward effects resulted from prolonged administration of compound RT to 85 patients, who took the drug continuously for periods of from six to twenty-six months. Temporary dryness of the throat and impaired appetite were rather common and may be ascribed to decreased salivary and gastrointestinal secretion. Initial loss of weight was frequent; its degree however, was never alarming; the weight curves usually leveled out after from two to six months. Slight constipation was a feature common

Fig. 4.—Notable improvement in the handwriting of a patient with postencephalitic parkinsonism after treatment with belladonna alkaloid compound RT and deterioration after compound RT was replaced by compound A. The first sample (*1*) was written before treatment, the second (*2*) one year later, during treatment with 3.0 mg. of compound RT, and the third (*3*) several days later, during treatment with 3.0 mg. of compound A.

to treated as well as to untreated parkinsonian patients. Treatment with compound RT relieved this symptom in some cases and made it worse in others. It was impossible to decide how much was due to the disease and its progression and how much to the effect of the drug. Apparently, the symptom is in part caused by the disease. Severe forms of constipation occurred in but 3 patients, in 2 of whom the symptom had preceded any treatment. Roentgenographic examination of the gastrointestinal tract of these 3 patients failed to reveal any pathologic condition. No signs of megacolon were found.

Belladonna alkaloid compound RT did not raise the pulse rate nor the blood pressure to any significant extent, as might have been expected.

In several patients with hypertension the blood pressure as well as the pulse rate decreased. Extrasystoles were encountered in 1 patient who had been taking very small amounts of compound RT, 0.75 mg. per day, for seven months. Whether or not a causal connection existed between the symptom and the drug could not be decided.

Excitement or hallucinations did not occur. A "light-headed" feeling, occasionally described by a few patients, disappeared after slight decrease in dosage.

Compound RT proved not to be habit forming. Once an optimum dose had been established, causing certain side effects, the same degree of severity of these effects usually followed the same dose for years and did not permit further increase in dosage.

Consequently, compound RT seems to be not only more effective but less toxic, and smaller amounts are required for optimum results than with the use of individual alkaloids, stramonium or other combinations of single alkaloids. The most acceptable explanation for these facts seems to be the assumption of a pharmacodynamic synergism of the alkaloids hyoscyamine, atropine and scopolamine when combined in a certain ratio as present in compound RT.

Extracts of Bulgarian and American belladonna roots have been compared with compound RT in a previous publication.[4] No appreciable difference between their effects was observed. Recently, Price and Merritt [15] arrived at the same conclusion. A contradictory statement of Neal and Dillenberg,[16] who compared the efficacy of "bellabulgara" [17] and compound RT, was refuted in a separate publication.[18] All preparations derived from belladonna roots have the disadvantages which have previously been mentioned for all natural extracts and stramonium, for example, lack of uniformity and stability.

Every patient with parkinsonism presents individual as well as typical clinical features. It might well be that excited patients respond better to a preparation containing a higher proportion of scopolamine and depressed or lethargic patients to one with a higher proportion of atropine. There are no doubt patients for whom individual adjust-

15. Price, J. C., and Merritt, H. H.: The Treatment of Parkinsonism: Results Obtained with Wine of Bulgarian Belladonna and the Alkaloids of the U. S. P. Belladonna, J. A. M. A. **117**:335 (Aug. 2) 1941.

16. Neal, J. B., and Dillenberg, S. M.: A Comparison of Bellabulgara and Other Forms of Medication in the Treatment of Chronic Encephalitis, New York State J. Med. **40**:1300, 1940.

17. "Bellabulgara" is a tablet containing 0.4 mg. of the total alkaloids extracted by white wine from the selected roots of Bulgarian belladonna.

18. Vollmer, H.: A Comparison of Synthetic and Natural Belladonna Alkaloid Compounds in the Treatment of Parkinsonism, New York State J. Med. **42**:1069, 1942.

ment of the alkaloid proportions is preferable to any rigid therapeutic principle. Nevertheless, for the great majority of patients with parkinsonism, compound RT proved more satisfactory than other alkaloid combinations or individual alkaloids which have been tried in the present comparative study.

SUMMARY

An alkaloid mixture consisting of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide (belladonna alkaloid compound RT) proved to be more effective in the treatment of parkinsonism, even in smaller amounts, than individual alkaloids, other combinations of individual alkaloids or stramonium.

The therapeutic index, i. e., the relation between the toxic and the therapeutic effect, of this compound seems to be higher than that of individual alkaloids or of other alkaloid combinations. No toxic manifestations resulted from prolonged administration of this compound.

The superiority of this compound is ascribed to a pharmacodynamic synergism of the three individual alkaloids when combined in a certain ratio.

Belladonna alkaloid compound RT is equivalent in its efficacy, and superior in uniformity and stability to preparations derived from Bulgarian or American belladonna roots.

25 Central Park West.

MYELOPATHY FOLLOWING COMPRESSION OF ABDOMINAL AORTA FOR POSTPARTUM HEMORRHAGE

REPORT OF A CASE

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AND
HERMAN A. STRAUSS, M.D.
CHICAGO

Studies on the effect of temporary occlusion of the abdominal aorta on the functions of the spinal cord have been almost exclusively limited to experimental animals. An unusual opportunity to observe these effects presented itself in a case in which one of us (H. A. S.) found it necessary to compress the abdominal aorta in order to control a severe postpartum hemorrhage. This recognized, but little used, obstetric procedure may be accomplished by various methods, one of which is the application of an abdominal tourniquet, the so-called Momburg tube. The Momburg tube is simply a length of thick rubber hose which is tightly applied around the abdomen just above the iliac crests. Little is known in this country about the possible harmful effects of this procedure. De Lee [1] cited a report by Pagenstrecker of ischemic paralysis of the distal end of the spinal cord. The following report deals with a case of myelopathy resulting from temporary aortic occlusion and is of neurophysiologic as well as clinical interest.

REPORT OF CASE

A married woman aged 35 was admitted to the obstetric service of the Michael Reese Hospital on May 8, 1940. She had had a normal full term pregnancy and entered the hospital in labor. Two previous pregnancies had resulted in the birth of normal full term infants. Five years previously she had had an abortion. The past history otherwise contained nothing of significance.

On examination a moderate amount of vaginal bleeding was noted. The blood pressure was 125 systolic and 90 diastolic and the pulse rate 86. Roentgenograms revealed the fetus to be in a transverse position. Rectal and sterile vaginal examinations showed the cervix to be dilated only 1 to 2 cm. Inasmuch as the

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Read at a meeting of the Chicago Neurological Society, Nov. 27, 1941.

From the Departments of Neuropsychiatry and Obstetrics of the Michael Reese Hospital.

1. De Lee, J.: Principles and Practice of Obstetrics, ed. 5, Philadelphia, W. B. Saunders Company, 1928.

uterine contractions were poor, a 9 cm. intraovular Vorhees bag was introduced and a 1 pound (453 Gm.) weight attached. Stronger uterine contractions then occurred. Meanwhile the vaginal bleeding increased, and on the morning of May 9 the patient showed signs of shock, with rapid pulse and a blood pressure of 75 systolic and 40 diastolic Serum and blood were given intravenously. Later in the morning the uterine cavity was entered, both feet were brought down, and subsequently a stillborn infant was delivered. A diagnosis of marginal lateral placenta praevia was made. After the delivery there was profuse bleeding which could not be controlled by intravenous injections of ergonovine hydrocrylate (ergotrate) and solution of posterior pituitary. The placenta was removed manually and the uterus packed several times, without avail. Despite intravenous administration of blood, serum and saline solution the patient's condition became critical. Inasmuch as she was pulseless, it was decided to compress the abdominal aorta as an emergency life-saving measure to control the uterine bleeding. This was accomplished by means of a Momburg tube applied around the abdomen at the level of the umbilicus. The hemorrhage was controlled but recurred when the tourniquet was released after forty-five minutes. The tube was then reapplied and kept in place intermittently, after which supracervical hysterectomy was performed. The total duration of this intermittent application of the tourniquet was two hours. Meanwhile the patient was treated in the usual way for hemorrhage and shock, receiving a total of 3,000 cc. of blood, serum and fluids intravenously, and hypodermic injections of morphine during this period. The first few days after operation the patient was very sick. The acute posthemorrhagic anemia, with red cells numbering 3,080,000 and a hemoglobin content of 50 per cent, rapidly improved with transfusions, so that by May 14 the red cell count was up to 4,500,000. Bronchopneumonia also developed and was treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and oxygen. Albuminuria appeared, and the urine contained red and white cells and granular casts. As the patient recovered from the posthemorrhagic shock and acute hemorrhagic anemia, the blood pressure returned to normal and in a few days became intermittently elevated to about 150 to 160 systolic and 100 diastolic. During subsequent weeks this hypertension became constant, with readings as high as 180 systolic and 120 diastolic. At no time was the nonprotein nitrogen content of the blood elevated.

As the patient's general condition improved during the first postoperative week, the neurologic disturbances in the lower extremities were noted. These disturbances evidently began within a relatively few hours after the application of the abdominal tourniquet (May 9), as the nurses noted a loss of sensation in both legs eleven hours later. Some movement in the legs was apparently present at this time. On May 10 the patient complained of pain in the lower extremities, and there was paralysis of both legs except for slight movement in the feet and ankles. She was seen by the neurologic consultant for the first time on May 16. Examination at that time revealed flaccid paraplegia, with absence of deep reflexes. Movement was present in the toes, and there were slight eversion, dorsiflexion of the feet and slight flexion of the thighs. Cutaneous sensibility was absent in both legs except on the soles of the feet, which were hyperalgesic. Incontinence of the bladder and bowels was present. The neurologic diagnosis was ischemia of the spinal cord due to interference with the blood supply.

Motor function improved progressively thereafter. Several days later sensation in the lower portions of the legs returned, but the upper lumbar and lower sacral segments remained severely involved. On May 23 the patient suddenly

complained of being unable to see or hear and then had a generalized epileptiform convulsive seizure, with loss of consciousness. According to the nurses, the seizure began in the right hand. After the attack the patient was confused and unable to answer questions or obey simple commands and had great difficulty in the use of words. A second convulsion occurred during the evening of the same day. For the next twenty-four hours she was confused, comprehension and thinking were impaired and she complained of inability to see. As far as could be determined, vision was present, so that it was felt that the disturbance was in the visual gnostic functions. Neurologic examination revealed no other focal signs. The following day she was rational but had little memory of the events of the preceding two days, and cerebration was still a little slowed. Vision was now good; the visual fields showed no gross defect. There was some difficulty in reading and writing but no impairment in speaking or comprehending spoken words. On attempting to write she showed perseveration. After several days these aphasic symptoms also disappeared completely. Apparently a vascular disturbance, associated with the hypertension, or embolization had occurred, the lesion involving the left parietal lobe in the region of the angular and supramarginal gyri.

By June 1 the patient's condition had improved so that all movements of the lower extremities were present, but there was still severe weakness of varying degrees in different muscle groups. Flaccidity was still present, and a plantar response was obtained on stroking the soles. Knee and ankle jerks were still absent, as were the abdominal reflexs. Cutaneous sensation involving all modalities was impaired below the level of the eighth thoracic segment anteriorly and the twelfth thoracic segment posteriorly. The lower sacral segments were not spared. Sensibility relative to the posterior column was intact. Control of the anal sphincter had returned, but urinary incontinence continued.

In addition to these neurologic disturbances there was persistent hypertension of 150 to 180 systolic and 110 to 120 diastolic. The urine still contained a little albumin and a few red and white cells per high power field, but there was no evidence of nitrogen retention. The medical consultants could not with any certainty explain the origin of this hypertension. Renal damage due to interference with the blood supply, associated with constriction of the aorta and retrograde thrombosis, was one of the possibilities discussed, but there was no conclusive clinical evidence of renal insufficiency. A hypothalamic lesion due to embolization was suggested. Another puzzling symptom was persistent tachycardia, the rate usually being between 110 and 130 per minute. An electrocardiogram was interpreted as probably abnormal, and digitalis was given for a month and then discontinued because of nausea and vomiting. The pulse rate dropped gradually to between 100 and 110 and returned to normal only after two months. The blood pressure also gradually diminished, so that by the end of July the systolic readings were normal but the diastolic pressure remained about 95 mm. The urine also slowly returned to normal.

Gradual and progressive improvement in muscle power was noted. Treatment consisted of physical therapy and exercises in the Hubbard tank. Considerable spontaneous pain and hyperpathia was present in the legs. By the end of July the patient was able to stand up and to walk with assistance. Because of a great deal of fear her progress was slower than the degree of disability warranted. On September 7 she felt and sustained a fracture of the lower end of the right fibula. At the time of discharge, on September 15, she was able to walk, but only with a guarded and cautious gait because of her fear of falling.

The sensory disturbances were still extensive, but normal cutaneous sensibility was now present in the perianal zone and in both feet. Posterior column sensibility was intact throughout. The patient was then followed in the Mandel clinic of the Michael Reese Hospital, treatment consisting of intensive physical therapy, to which she responded with gradual but progressive improvement. There was considerable urinary difficulty, with frequency and terminal hematuria. Cystoscopic examination revealed a bladder of normal capacity and a bean-sized, bulbous area of edema, the center of which was necrotic and incrusted, over the right ureteral orifice. The patient was rehospitalized in February 1941, and the lesion was fulgurated. A biopsy specimen of the tumor-like mass proved to be inflammatory tissue, and a diagnosis of granuloma of the bladder was made. The patient has continued to receive treatment for this lesion, consisting of instillations and a second fulguration in October 1941.

At the time of the last examination, in November 1941, the neurologic status was as follows: The gait was somewhat guarded, owing to a conscious fear of falling, but was otherwise normal. The patient was afraid to walk rapidly. Objectively, the motor power in both lower extremities was excellent, and there were no muscular atrophies. There was no spasticity; if anything, slight hypotonicity was present. Knee and ankle jerks were absent on both sides. Plantar flexion of the big toe was present bilaterally. Subjective and objective sensory disturbances were present below the groins bilaterally. The patient complained of spontaneous "soreness" over the anterior surfaces of the thighs. The objective sensory disturbances involved mainly the first four lumbar segments bilaterally, although the fifth lumbar and the first, second and third sacral segments were slightly involved. There were hypesthesia over the anterior surfaces of both thighs and legs, hyperalgesia and hyperpathia in the same areas, except for the right leg, which was hypalgesic, and thermhypesthesia posteriorly as well as anteriorly over both legs. Deep sensibility was intact throughout. Sensation in the perianal zone and over the buttocks was normal. Coordination in the lower extremities was good; there was no ataxia. Bowel function and control were good, but some urinary urgency was still present, with incontinence at times.

COMMENT

The neurologic disturbances in the lower extremities were evidently due to acute interference with the blood supply to the spinal cord and nerve roots as a result of the compression of the abdominal aorta. To understand the pathophysiologic process it is necessary to review briefly the anatomy of the blood supply of the spinal cord. Posterior and anterior radicular arteries, branching off from the intercostal, lumbar, sacral and vertebral arteries, accompany the nerve roots through the intervertebral foramens. According to Suh and Alexander,[2] only a certain number of these anterior radicular arteries join the anterior spinal artery, which descends the whole length of the cord from its origin at the vertebral arteries. According to their observations, these arteries are distributed as follows: one or two to the lumbar, one to the lower

2. Suh, T. H., and Alexander, L.: Vascular System of the Human Spinal Cord, Arch. Neurol. & Psychiat. **41**:659 (April) 1939.

thoracic, none or one to the middle thoracic, one or two to the upper thoracic and one to three to the cervical region. The largest vessel is in the lumbar region, the arteria radicularis magna, which usually enters at the second lumbar segment but may enter anywhere from the eighth thoracic to the fourth lumbar segment. It is evident therefore that the relatively great distance between these segmental sources of blood supply makes the spinal cord vulnerable to ischemia despite the collateral vascular supply from the anterior spinal branch of the vertebral arteries and from the radicular branches of the intercostal arteries. The lower thoracic segments of the cord are especially vulnerable, as they receive most of their segmental blood supply from above and below. Another anatomic feature of importance is the variability in the anatomic location of the large lumbar radicular artery, which may enter as low as the fourth lumbar segment and which apparently contributes quantitatively a great deal to the arterial blood supply of the lower portion of the cord. Recently Suh and Alexander [2] have shown, as did Tanon as far back as 1908, that injection of the anterior spinal artery in the sacral region resulted in injection of the entire cord. These authors claimed, however, that the blood supply of the cord depends mainly on these relatively few radicular arteries and that myelomalacia may as a result exist far beyond the site of vascular occlusion. In view of these anatomic features it is possible to understand the extensive involvement of the lower thoracic and lumbosacral portions of the cord in the case herein reported, despite the fact that the compression of the aorta occurred at the level of the umbilicus, i. e., approximately opposite the third lumbar vertebra, a point below the termination of the spinal cord proper.

The neurologic findings point to involvement especially of the anterior half of the cord, inasmuch as sensitivity relative to the posterior column was spared. Except for the involvement of touch sensation, the picture fits in with that typical of occlusion of the anterior spinal artery, namely, flaccid paraplegia, loss of reflexes, absence of defense reactions, dissociated sensory loss and bladder and bowel dysfunction.[3] In our case touch sensation was involved, suggesting a more extensive pathologic process, affecting possibly the posterior column. The selective involvement of the anterior half of the cord with sparing of the posterior half has a sound anatomic basis, as the circulation of the posterior part of the cord does not depend on so few arteries as does the anterior portion. It is probable that lesions also exist in the lumbosacral spinal ganglia and nerve roots, as they receive their blood supply segmentally through the radicular arteries from various branches of the abdominal aorta. The cutaneous dysesthesia and hyperpathia may be explained on

3. Zeitlin, H., and Lichtenstein, B. W.: Occlusion of the Anterior Spinal Artery, Arch. Neurol. & Psychiat. **36**:96 (July) 1936.

this basis. According to a recent study by Bergmann and Alexander,[4] the arterial supply of the spinal ganglia may be considered to be rather vulnerable.

Experimental studies on the effects of total temporary aortic compression on the spinal cords of animals have been carried out, most recently by Tureen,[5] to whose excellent histologic studies the reader is referred. The clinical disturbances seen in our patient are comparable for the most part to the results of occlusion of the thoracic aorta in experimental animals, namely, paraplegia, bladder and bowel paralysis and sensory disturbances. In cats, however, the paraplegia is only initially flaccid, with areflexia, spasticity and hyperreflexia developing ten to thirty minutes after operation. In our case, as in most cases of occlusion of the anterior spinal artery in man,[3] the paraplegia remained flaccid. Tureen and other previous workers demonstrated that the degree of reversibility of the physiologic and histologic disturbances depends mainly on the duration of the vascular occlusion. In cats in which the thoracic aorta had been occluded for not more than fifteen minutes the paraplegia disappeared rapidly and the animals could walk in twenty-four hours. Motor power did not reappear in animals in which occlusion lasted twenty minutes or longer. Histologic study of the lumbar portion of the spinal cord subjected to only fifteen minutes of vascular occlusion failed to reveal any pathologic changes. Obviously, experimental results in the cat cannot be applied to man, but it is of comparative anatomic interest that in the cat clamping of the abdominal aorta as high as the left renal artery fails to produce ischemia of the cord, indicating the competence of the collateral circulation from above. The clinical findings in our single case and in Pagenstrecker's case following compression of the lower end of the abdominal aorta, as cited by De Lee,[1] tend to confirm Suh and Alexander's [2] anatomic observations on man regarding the importance of the segmental aortic supply to the spinal cord and the inadequacy of the collateral circulation from above. One cannot be certain whether or not some blood leaked beyond the point of compression, although the complete cessation of uterine bleeding is suggestive of complete occlusion. Despite the long period of aortic compression (forty-five minutes and then intermittently, a total of two hours), the pathologic alterations in the spinal cord must have been largely reversible, as there has been complete return of motor power. This restitution of function indicates that sufficient collateral circulation from above was operating to prevent complete

4. Bergmann, L., and Alexander, L.: Vascular Supply of the Spinal Ganglia, Arch. Neurol. & Psychiat. **46**:761 (Nov.) 1941.

5. Tureen, L. L.: Effect of Experimental Temporary Vascular Occlusion on the Spinal Cord, Arch. Neurol. & Psychiat. **35**:789 (April) 1936.

destruction of the neural elements in the involved segments and that aortic compression can probably be carried out for shorter periods, such as fifteen or twenty minutes, with comparative safety. The persistence of sensory disturbances and the areflexia indicate that pathologic alterations are still present and that further observation in this case will probably reveal an unpredictable degree of irreversible residual disturbance.

SUMMARY

A case of severe myelopathy following compression of the abdominal aorta for the control of a postpartum hemorrhage is described. Despite the prolonged aortic compression, the resulting paraplegia disappeared over a period of months, but certain sensory disturbances persisted. Certain significant anatomic features of the vascular supply of the spinal cord are discussed.

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104 South Michigan Avenue.

DISCUSSION

DR. PERCIVAL BAILEY, Chicago: I understand Dr. Levy to say that paralysis was noted eleven hours after operation and that when the neurologist saw the patient it had increased. Did I understand correctly, and, if so, how is it to be explained?

DR. NORMAN A. LEVY, Chicago: I think Dr. Bailey misunderstood me. The neurologic consultant did not see the patient for a week. The nurses were the first to notice that there was lack of feeling in the legs, but the patient was so sick that the neurologic disturbances had to be disregarded.

As to thrombosis, we thought originally the cause might be retrograde thrombosis of the arteries higher up, but on the basis of the recovery I concluded it was ischemia rather than thrombosis.

CENTRAL AUTONOMIC PARALYSIS

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Observations on the disturbances in sensory and motor functions produced by lesions in the brain and spinal cord in man have been of great aid in determining the motor and sensory pathways in the central nervous system. A study of the disturbances in the function of the autonomic nervous system produced by lesions in the brain and spinal cord should yield information concerning the autonomic pathways in the central nervous system. Because disturbances in autonomic function are more difficult to evaluate than the sensory and motor disturbances produced by lesions in the central nervous system, observations on central autonomic paralysis in man are few and incomplete. Those that are available are usually confined to one function of the autonomic nervous system, the study of sweating being the most common. The purpose of this paper is to describe the clinical picture of central autonomic paralysis and by a study of several functions of the autonomic nervous system to show how central autonomic paralysis may differ from the type of paralysis produced by section of the sympathetic chain or of a peripheral nerve.

Six patients who had had more or less typical lateral medullary lesions were studied. The case histories of the 2 patients presenting the most extensive disturbances in autonomic function are presented in detail. Those of the other 4 are briefly summarized.

REPORT OF CASES

CASE 1.—A. M., a 58 year old spinster, a hairdresser was admitted to the Peter Bent Brigham Hospital on March 13, 1941, with the presenting complaints of dizziness and headache. For one year previous to admission she had experienced fatigue, irritability, occipital headaches and occasional light headedness. She consulted her physician, who told her that she had hypertension.

Part of the expense of this investigation was defrayed by the Milton Fund.

From the Medical Clinic of the Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

Two weeks before admission she felt unusually dizzy and nauseated and reeled drunkenly. She had pain over the left eye; on looking into a mirror she was astonished to see that the left eye was smaller than the right. Later she vomited. On awakening the next morning, in addition to the aforestated symptoms, she felt as though the right side of her body had been packed in ice. On arising she consistently fell to the left. She also complained of weakness of her right arm and leg and of occasional knifelike pains in her right thigh and leg. She had minimal difficulty in articulation but none in deglutition. The severity of her symptoms remained unchanged for three days. At this time the vomiting stopped and the other symptoms decreased gradually. She sought relief from her symptoms, without success, and eventually was admitted to the hospital.

Physical examination revealed a large, obese, well nourished woman. The blood pressure was 160 systolic and 100 diastolic. The apex impulse of the heart was felt in the midclavicular line. The cardiac sounds were regular and of good quality. There were no murmurs. The chest was clear. Routine analysis of blood and urine revealed nothing significant.

Neurologic examination showed the following changes: The optic disks appeared normal. However, the retinal arteries were tortuous, with marked arteriovenous nicking. The left pupil was smaller than the right, measuring 2 mm. in diameter, as compared with the right, which was 5 mm. Both pupils reacted promptly to light and in accommodation. The extraocular movements were within normal limits, and there was no nystagmus. There were slight ptosis and enophthalmos of the left eye. Cotton wisp, pinprick and ice were appreciated equally well on the two sides of the face. Both corneal reflexes were present. There was no demonstrable weakness in the volume or strength of the masseter muscles. There was slight weakness of the lower right side of the face, accentuated with voluntary grimacing. Examination of the drums revealed thickening on both sides. There was bilateral impairment of hearing, being greater on the left than on the right. With a history of bilateral otitis media it was difficult to ascertain whether she had left nerve deafness superimposed on her previous conduction deafness. On most occasions she lateralized the sound of the tuning fork to the right. The palate was elevated in the midline; her voice showed questionable thickening. There was no evidence of dysfunction of the eleventh or twelfth cranial nerve.

The patient swayed when she was asked to stand. On a number of occasions she fell to the left from the Romberg position. Finger to nose and finger to finger tests showed slight weakness on the right side and ataxia on the left. The volume of the muscles was not decreased on either side of the body. There was weakness of the right side of the body, as evidenced by sway of the right hand and by a positive Barré reaction. The deep reflexes were increased on the right side as compared with those on the left. The plantar reflex on the right was extensor. There was ataxia in the heel to knee test on both sides, although the incoordination was more noticeable on the left. There was questionable evidence of disturbed appreciation of form and texture in the right hand. Hypalgesia and thermhypesthesia were present on the right side of the body up to the face. A questionable disturbance of vibration sensibility was noted on the right side. There was an objective difference in temperature of the two sides of the body in a cold room, the right side being colder than the left. Touch sense was not disturbed on either side of the body.

At no time in the prodromal period or during the course of her illness did the patient lose consciousness. At the time of examination she was aware and attentive

and displayed no evidence of aphasia. She was pleasant and successful in her work, and her reaction to her illness and her disability was quite within normal limits.

Lumbar puncture revealed an initial pressure of 160 mm. of water, with adequate rise and fall with jugular and abdominal pressure and a final pressure of 100 mm. after 15 cc. of fluid was removed. The fluid was clear and colorless and had 2 lymphocytes and 31 red cells per cubic millimeter. The total protein was 13 mg. per hundred cubic centimeters. The serologic reactions were negative.

Electroencephalographic studies revealed periods of disorganized frequency, with both rapid and slow activity, there being few normal frequency cycles. Localization studies failed to show any focal cortical dysrhythmia. The changes described were uniformly distributed over both hemispheres.

The patient was discharged to her home on the forty-fourth day in the hospital, April 15, with a diagnosis of hypertensive cardiovascular disease with hypertensive headache and thrombosis of an atypical branch of the left posterior inferior cerebellar artery or of the left superior cerebellar artery, due to arteriosclerosis. When she was last seen, in March 1942, her condition was essentially unchanged.

CASE 2.—J. K., a housewife aged 58, was admitted to the Peter Bent Brigham Hospital on Dec. 4, 1941, with the presenting complaints of weakness, nausea, vomiting, headache, singultus, vertigo and tinnitus in her left ear. She had a history of hypertensive cardiovascular disease. On the evening before admission she appeared to be well, but the next morning on awakening she experienced the aforestated presenting symptoms.

On admission the chest seemed clear on percussion and auscultation. The heart was considerably enlarged to the right, with the apex impulse in the axilla. The rate was 80; the rhythm regular; the blood pressure 270 systolic and 135 diastolic.

The vital signs were within normal limits. Routine examination of the blood and urine revealed nothing significant except minimal albuminuria. The spinal fluid was under an initial pressure of 210 mm. of water and was clear and colorless; the dynamics were normal. There were 1 lymphocyte and 200 fresh red blood cells per cubic millimeter. The serologic reactions were negative, and the colloidal gold curve was normal. The total protein was 33 mg. per hundred cubic centimeters. Roentgenograms of the skull showed marked calcification of the internal carotid arteries.

Examination revealed the following pertinent neurologic signs: There was a Horner syndrome on the left side, with miosis (left pupil 2 mm., right pupil 5 mm., in diameter), ptosis, increased warmth and decreased sweating of the face. There were increased warmth and decreased sweating over the left side of the trunk and the left extremities. Nystagmus was present on lateral and vertical gaze. The left corneal reflex was absent, and there were hypalgesia and hypthermesthesia of the left side of the face. There were slight weakness of the left side of the face and thickness of speech. The left arm and leg were weak and were ataxic in finger to nose, heel to knee and toe to object tests. There were hypalgesia and hypthermesthesia of the right side of the trunk and the right extremities. There was no evidence of disturbance in the peripheral nerves or the posterior column. The plantar responses were flexor.

With the sudden onset of nausea, vomiting, vertigo and singultus and with neurologic signs of ipsilateral involvement of the intramedullary autonomic pathway, the descending tract of the nucleus of the fifth nerve, the nucleus of the

seventh nerve, the nucleus ambiguus and the restiform body and contralateral involvement of the spinothalamic tract, the diagnosis of a typical lateral medullary syndrome due to arteriosclerotic thrombosis of the left posterior inferior cerebellar artery was made.

The nausea, vomiting, singultus and vertigo gradually subsided. The patient improved in strength and, after certain investigative procedures were carried out, was discharged on the thirty-sixth day in the hospital (Jan. 7, 1942), with no essential change in her neurologic condition.

The final diagnosis was arteriosclerotic thrombosis of the left posterior inferior cerebellar artery and hypertensive cardiovascular disease. The patient was last seen in February 1942, at which time she was continuing to improve in strength, although her neurologic condition showed no essential change.

CASE 3.—G. P., a 52 year old Negro, had had a typical lateral medullary lesion due to thrombosis of the right posterior inferior cerebellar artery in 1933. When he was studied in 1941, he had a small right pupil, with minimal ptosis and enophthalmos on the same side. There was diminished sweating over the right side of the face, the right arm and the right side of the trunk, but no abnormality of sweating over the lower extremities. The blood flow in the hands increased and decreased equally in a normal manner when the body was heated or cooled, and the vasomotor responses to sensory stimuli were normal. The cutaneous temperatures on the two sides were not measured, but no difference was detectable by palpation.

CASE 4.—B. D., a 53 year old white man, had had thrombosis of the right posterior inferior cerebellar artery in 1934. In 1941 he showed no evidence of Horner's syndrome. There was hyphidrosis of the right side of the face and the right upper extremity. Neither the cutaneous temperature nor the blood flow was studied. There were no detectable differences in cutaneous temperature on palpation.

CASE 5.—A 50 year old man had had thrombosis of the left posterior inferior cerebellar artery in 1937. In 1941 questionable ptosis of the left eyelid was the only residual sign of his previously noted Horner syndrome. Sweating was equal on the two sides. There was no difference in cutaneous temperature or in the blood flow of the extremities on the two sides. The blood flow in the hands increased and decreased normally as the body was heated or cooled.

CASE 6.—J. M., a 60 year old man, had had thrombosis of a lateral branch of the left posterior inferior cerebellar artery. He was examined one year after his illness, when minimal ptosis was the only residuum of the preexisting Horner syndrome. Objectively, there was no disturbance of vasomotor function in the hands or of sweating on either side of the body.

In both case 1 and case 2 the Horner syndrome on the left and the obvious difference in temperature of the right and left extremities suggested that the autonomic nervous system had been affected by the lesion in the brain stem. The following studies were carried out in these 2 cases to determine the extent of the involvement of the autonomic nervous system and whether all of the functions of the autonomic nervous system were equally involved.

A. Sweating.—The disturbance in sweating was similar in the 2 cases. On heating the body, there was a distinct difference in sweating

on the two sides. Sweat appeared earlier over the entire right side of the body and face. After vigorous heating sweat appeared on the left side of the trunk and the left lower extremity. Later perspiration was also visible over the left side of the face and the left upper extremity. After further heating the lower extremities were equally wet, but perspiration over the left side of the trunk and face and the left arm was still noticeably less than over the corresponding areas on the right side.

B. Cutaneous Temperature After Heating and Cooling the Body.—In both cases abnormalities in the left arm and leg on heating and cooling the body were noted. In a cool room the left arm and leg were warmer than the right. In a warm room the temperatures of the extremities became equal. The following experiment was carried out in case 1 (fig. 1). The patient was placed in a cool room (temperature

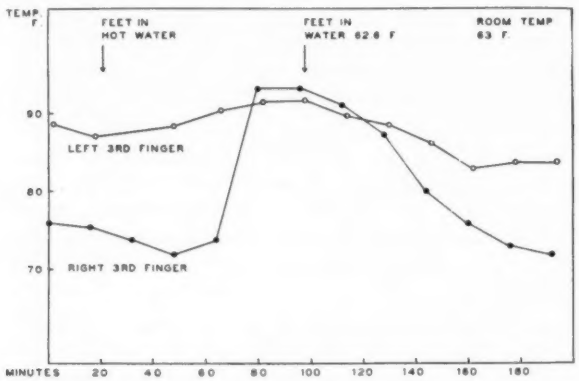

Fig. 1 (case 1).—Changes in cutaneous temperature of the digits produced by heating and cooling the body. The response in the right third finger is normal. The response in the left third finger indicates inability of the blood vessels to constrict normally when the body is cooled.

63 F.), and the cutaneous temperatures of the terminal phalanges of the middle fingers were recorded. The left hand was warmer than the right. The patient's feet and legs were then immersed in hot water (109 F.). Forty-four minutes later the temperature of the right hand had increased, and at the end of sixty minutes the temperatures of the digits of the two hands were about the same. Twenty-four minutes after full vasodilatation had occurred, the patient's legs and feet were immersed in water at a temperature of 63 F. The temperature of the right middle digit fell rapidly to the preheating level; that of the left fell more slowly to below the preheating level, although the left digit remained about 10 degrees (F.) warmer than the right.

In case 2 the cutaneous temperatures of the right and left third fingers and of the right and left first toes were recorded (fig. 2). In a cool room (62 F.) the skin of the left finger and toe remained abnormally warm, while that of the right finger and toe became normally cold. The body was then heated with a light cradle for sixty minutes. The cutaneous temperature of the right finger and toe rose rapidly. At the end of the period of body heating the cutaneous temperatures of the digits of the right and the left extremity were approximately equal.

C. Effect of Heating and Cooling the Body on the Blood Flow in the Hand and Foot.—The blood flow in the hands and feet was measured by plethysmographic methods and recorded in cubic centimeters of flow per minute per hundred cubic centimeters of tissue.[1] In case 1 (fig. 3 *B*)

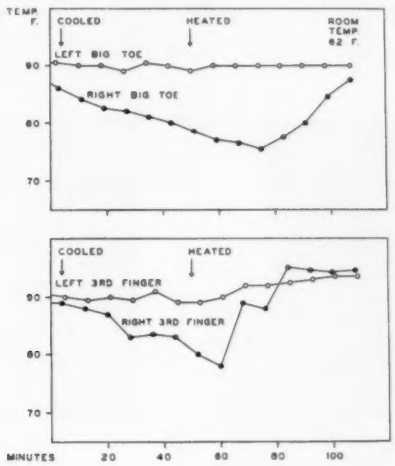

Fig. 2 (case 2).—Changes in cutaneous temperature of the digits produced by cooling and heating the body. The responses in the right big toe and in the right third finger are normal. The responses in the left big toe and the left third finger demonstrate that the blood vessels do not constrict normally when the body is cooled.

the hands were placed in water at a temperature of 88 F. The extremities were exposed and the trunk was lightly covered. The room temperature was 70 F. After thirty minutes the blood flow in the left hand was 6 cc. and that in the right hand 1 cc. After seventy-five minutes of heating the blood flow in the left hand was 15 cc. and that in

1. Freeman, N. E.: Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**:384 (Oct.) 1935. Stead, E. A., Jr., and Kunkel, P.: A Plethysmographic Method for the Quantitative Measurement of the Blood Flow in the Foot, J. Clin. Investigation **17**:711 (Nov.) 1938.

the right hand 14 cc. (fig. 3 *C*). In case 2 the blood flow in the hands was determined under similar conditions. When the patient was cool the blood flow in the left hand was 8 cc. and that in the right 3 cc. On

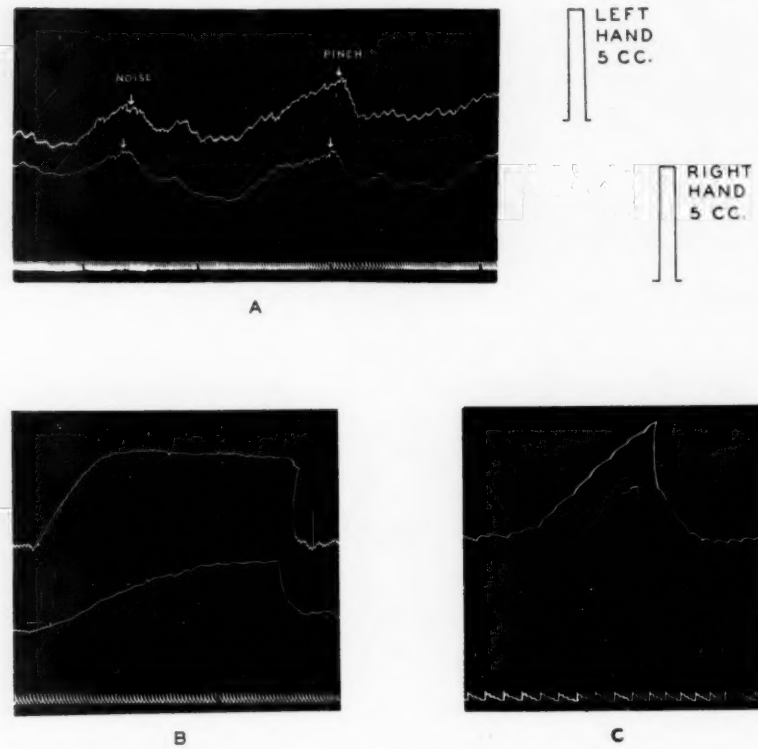

Fig. 3.—Plethysmographic studies of the vasomotor reactions and blood flow in the hands (upper tracing, left hand; lower tracing, right hand). In this and in figure 4, an increase in volume of the part is indicated by an upstroke and a decrease by a downstroke. The time is marked in seconds.

A, spontaneous variations in vasomotor tone. Noise and pinching produced equal degrees of vasoconstriction in the two hands. The temperature of the water in the plethysmograph was 88 F. The body was heated at the time tracings were taken.

B, blood flow in the left and the right hand with the body cool. The temperature of the water in the plethysmograph was 88 F.; the room temperature was 70 F. The steeper the slope of the curve, the faster the rate of increase of blood flow. The blood flow in the left hand was 6.2 cc. per hundred cubic centimeters per minute, the blood flow in the right hand was 1.4 cc.

C, blood flow in each hand after the body was heated. The temperature of the water in the plethysmograph was 88 F. The blood flow in the left hand was 14.5 cc. per hundred cubic centimeters per minute, and the blood flow in the right hand was 14.3 cc. There was no disturbance in vasodilatation in response to heating the body.

heating the body the blood flow became equalized in the two hands at a level of 15 cc.

Similar experiments were performed on the feet. The temperature of the water in the plethysmograph was 88 F., and the temperature of the room was 68 F. After thirty minutes the blood flow in the left foot in case 1 was 0.8 cc. and that in the right foot was 0.4 cc. (fig. 4 *B*). After heating the body the blood flow was 3.1 and 3.5 cc., respectively, in the left and the right foot (fig. 4 *C*). In case 2 the blood flow in the left foot was 1.1 cc. and that in the right foot was 0.6 cc. when the patient

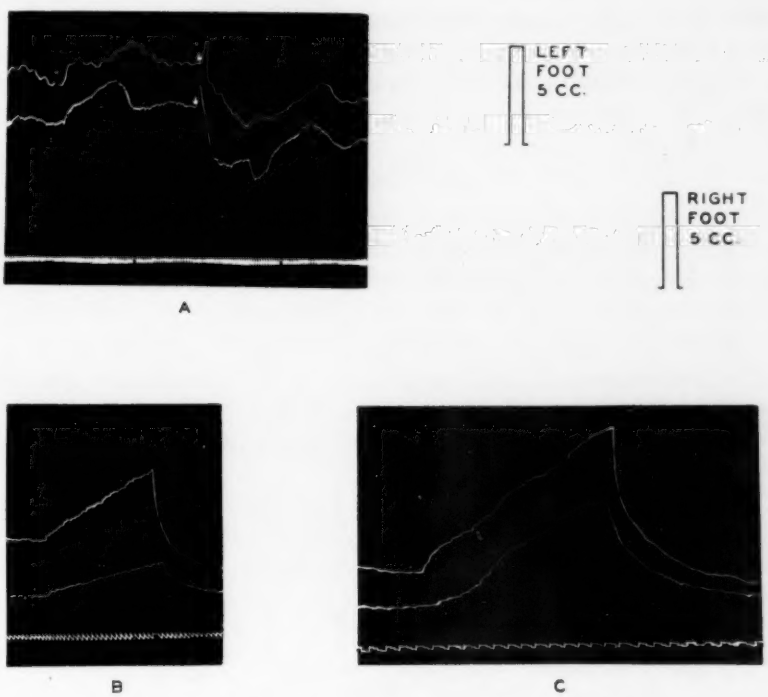

Fig. 4.—Plethysmographic studies of the vasomotor reactions and blood flow in the feet (upper tracing, left foot; lower tracing, right foot).

A, spontaneous variations in vasomotor tone. The marked vasoconstriction was caused by a deep inspiration at the point indicated by the arrows.

B, blood flow in the left and the right foot with the body cool. The temperature of the water in the plethysmograph was 88 F.; the room temperature was 68 F. The blood flow in the left foot was 0.8 cc. per hundred cubic centimeters per minute; the blood flow in the right foot was 0.4 cc.

C, blood flow in each foot after heating the body. The temperature of the water in the plethysmograph was 88 F. The blood flow in the left foot was 3.1 cc. per hundred cubic centimeters per minute; the blood flow in the right foot was 3.5 cc. There was no disturbance in vasodilatation in response to heating the body.

was cool. After heating the body the blood flow rose to a level of 2 cc. in the right foot and 2.5 cc. in the left.

D. Vasomotor Reflexes in the Hands and Feet in Response to Deep Inspiration, Noise and Pinch.—The vasomotor reflexes in cases 1 and 2 were investigated by plethysmographic methods. The water in the plethysmograph was maintained at a temperature of 88 F. The vasomotor responses were studied while the body was being heated, because it is difficult to compare the vasomotor reflexes in both hands or feet unless the same degree of vasodilatation is present on the two sides. Similar results were obtained in the two cases. The normal spontaneous fluctuations in the volume of the hands and feet were present bilaterally. Deep inspiration, noise or pinching the skin produced an equal degree of vasoconstriction in the right and in the left hand (fig. 3 *A*). Similar results were obtained when the vasomotor reflexes in the feet were tested (fig. 4 *A*).

COMMENT

The syndrome of occlusion of the posterior inferior cerebellar artery is characterized by homolateral signs of cerebellar involvement (restiform body); analgesia and thermanesthesia of the face and corneal hypalgesia (descending tract of the nucleus of the fifth nerve); Horner's syndrome (intramedullary sympathetic pathway); paresis or paralysis of the soft palate and vocal cord (nucleus ambiguus), and contralateral analgesia and thermanesthesia of the trunk and extremities (spinothalamic tract). Vertigo, nystagmus, deafness and singultus may also result from the lesion.

For descriptive purposes the signs and symptoms arising from this lesion are called the lateral medullary syndrome. It is usually due to involvement of the medial branch of the posterior inferior cerebellar artery, which supplies the dorsolateral part of the medulla oblongata. In cases 2, 3, 4 and 5 the lesion produced the typical signs and symptoms of the lateral medullary syndrome. In case 6 a lateral branch of the artery was probably implicated, as there was extensive involvement of the nucleus of the eighth nerve and the restiform body.

In case 1 the signs and symptoms, though indicating a lesion of the left side of the brain stem, were not those usually produced by thrombosis of the posterior inferior cerebellar artery. The clinical picture suggested the diagnosis of occlusion of a lateral branch of the left superior cerebellar artery, as that would better explain the contralateral signs of involvement of the pyramidal tract and medial lemniscus and the absence of ipsilateral involvement of the nucleus of the fifth nerve.

The syndrome of occlusion of the superior cerebellar artery is characterized by ipsilateral cerebellar dysfunction (involvement of the

cerebellar lobes or the brachium conjunctivum), tremor (involvement of the dentate nucleus) and contralateral hypalgesia and hyptherm-esthesia of the face and body (spinothalamic component of the medial lemniscus in the pontile tegmentum). Disturbance of the autonomic pathways (Horner's syndrome) and of the medial lemniscus has been reported in instances of occlusion of the superior cerebellar artery.[2]

Except in case 1, it is probable that the signs and symptoms of autonomic disturbance arose from a lesion of the autonomic pathway in the lateral reticular formation of the medulla. In case 1 the lesion may have been in the tegmental region of the pons.

In these 6 cases of thrombosis of the posterior inferior cerebellar artery, the degree of involvement of the autonomic nervous system varied greatly. In cases 5 and 6 only minimal ptosis of the ipsilateral eyelid was present. In case 3 there was a Horner syndrome, with hyphidrosis of the face, arm and trunk on the same side. In case 4 only hyphidrosis of the ipsilateral half of the face and upper extremity was evident. In cases 1 and 2 involvement of the autonomic nervous system was most extensive, with Horner's syndrome, hyphidrosis of the ipsilateral half of the body and disturbance in heat regulation.

In none of the 6 cases was the sympathetic paralysis complete. The lesion in the brain stem interfered with some, but not all, of the functions of the autonomic nervous system. In cases 1 and 2 vasoconstriction in response to cooling the body and sweating were seriously disturbed, but vasodilatation in response to heating the body and vasoconstriction in response to sensory stimuli, such as noise, pinch and deep inspiration, were unaffected. Observations on the pilomotor response to cooling the body were unsatisfactory. This picture is different from that produced by section of the preganglionic rami or by removal of the sympathetic ganglion. In cases of such lesions all functions of the autonomic nervous system are lost in the affected part. The blood flow and the temperature of the sympathectomized extremities are not influenced by heating or cooling the body; sweating does not occur when the body is heated, and vasoconstriction is not produced by pinch, noise or deep inspiration.

Sweating, though decreased in 4 cases, was never completely absent. List and Peet [3] studied the disturbances in sweating in cases of medullary lesions and of hemisection of the cord. They noted the presence of

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2. Davison, C.; Goodhart, S. P., and Savitsky, N.: Syndrome of the Superior Cerebellar Artery and Its Branches, Arch. Neurol. & Psychiat. **33**:1143 (June) 1935. Freeman, W., and Jaffe, D.: Occlusion of the Superior Cerebellar Artery, ibid. **46**:115 (July) 1941.

3. List, C. F., and Peet, M. M.: Sweat Secretion in Man: V. Disturbances of Sweat Secretion with Lesions of Pons, Medulla and Cervical Portion of Cord, Arch. Neurol. & Psychiat. **42**:1098 (Dec.) 1939.

hyphidrosis on the side of the lesion, but, as some sweating always occurred if the body heating was sufficiently intense, they concluded that the autonomic sweat fibers were both crossed and uncrossed. They further concluded that the cephalic sweat fibers form a distinct ipsilateral bundle in the lateral part of the medulla oblongata, for marked ipsilateral hyphidrosis of face and neck was demonstrable with very small lesions. They expressed the belief that the sweat fibers for the lower extremities may occupy a more medial position, for hyphidrosis of the lower half of the body was apparently more marked with large lesions extending farther medially.

In a cool room the increased temperature of the left arm and leg in cases 1 and 2 resulted from partial paralysis of the vasoconstrictor reflexes which normally conserve heat when the body is cooled. Though this disturbance was striking in both instances, it was somewhat more pronounced in case 2.

There was no disturbance in the vasodilator response to heating the body in either case. Before the body was heated the cutaneous temperature was higher and the blood flow was greater on the side of the lesion. When the body was heated the blood flow increased normally in all extremities, and after a time it was the same on the two sides. This response is in striking contrast to that which occurs after peripheral sympathectomy. After either preganglionic or postganglionic sympathectomy the blood flow in the affected extremity is not influenced by heating or cooling the body. When the body is exposed in a cool room the sympathectomized extremity is warmer than the normal extremity, but when the body is clothed and warm the blood flow in the sympathectomized part does not increase as it does in the normal extremity and the sympathectomized extremity becomes the cooler.[4]

The fact that the lesion in the brain stem had produced in 2 patients a unilateral disturbance in vasoconstriction in response to cooling the body without producing any detectable disturbance in vasodilatation in response to heating the body suggested the following possible interpretations: (*a*) The sympathetic nerves contain both vasoconstrictor and vasodilator fibers, and the medullary lesion had destroyed the central connections of the vasoconstrictor fibers without injuring the tracts concerned with vasodilatation; (*b*) the sympathetic nerves contain only vasoconstrictor fibers, vasodilatation being simply inhibition of vasoconstriction, so that partial destruction of the central connections of the vasoconstrictor fibers interfered with the active process of vasoconstriction without disturbing the passive vasodilatation resulting from

4. Wilkins, R. W., and Eichna, L. W.: Blood Flow to the Forearm and Calf: I. Vasomotor Reactions; Role of the Sympathetic Nervous System, Bull. Johns Hopkins Hosp. **68**:425 (June) 1941.

inhibition of vasoconstriction. Data may be obtained from the literature [5] to support either hypothesis, but recent experiments on normal subjects have suggested that the latter explanation is correct.[6] Cooling the body produces partial vasoconstriction either because the lesion in the medulla is not large enough to destroy all of the tract concerned with vasoconstriction or because some vasoconstrictor fibers cross from the opposite side below the lesion. These remaining connections are not able to produce complete vasoconstriction on cooling the body, but they do prevent the vessels of the extremities from exhibiting the increase in tone which follows either preganglionic or postganglionic sympathectomy. Thus, inhibition of vasoconstriction still produces full normal vasodilatation.

The spontaneous fluctuations in volume of the hand and foot, which are present in normal subjects and are absent after sympathectomy, were equal on the two sides. The vasoconstrictor responses to sensory stimulation or to a deep inspiration, which disappear after sympathectomy, were also equal on the two sides. The observations in cases 1 and 2 demonstrate that vasoconstriction to one stimulus, namely, cooling the body, may be impaired without any disturbance in vasoconstriction from other stimuli. The available evidence suggests that the spinal cord or the sympathetic ganglia do not supply the necessary reflex arc for the vasoconstriction produced by sensory stimuli. Bolton, Williams and Carmichael [7] studied 2 cases in which the lower portion of the spinal cord was destroyed but in which the sympathetic ganglia were intact. The fact that sensory stimulation of the area supplied by a destroyed portion of the cord produced no sympathetic responses was interpreted as indicating that there were no ganglionic vasomotor responses. Marquis and Williams [8] concluded that in man the vasomotor reflex arc concerned with vasoconstriction from sensory stimuli is complete in the brain stem below the level of the sensory thalamus. They expressed the belief, however, that the medullary center is not adequate for mediation of vasoconstrictor responses to sensory stimuli

5. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, Heart **16**:33 (Oct.) 1931. Grant, R. T., and Holling, H. E.: Further Observations on the Vascular Responses of the Human Limb to Body Warming: Evidence for Sympathetic Vasodilator Nerves in the Normal Subject, Clin. Sc. **3**:273 (Aug.) 1938.

6. Warren, J. V.; Walter, C. W.; Romano, J., and Stead, E. A., Jr.: To be published.

7. Bolton, B.; Williams, D. J., and Carmichael, E. A.: Sympathetic Ganglionic Responses in Man, Brain **60**:39 (March) 1937.

8. Marquis, D. G., and Williams, D. J.: The Central Pathway in Man of the Vasomotor Response to Pain, Brain **61**:203 (June) 1938.

in man, for lesions of the sensory pathway above the level of the medullary center caused marked alteration of the magnitude of the vasoconstrictor response.

Duthie and Mackay [9] studied the cutaneous temperature responses to heating and cooling the body in a patient with thrombosis of the left posterior inferior cerebellar artery. There were miosis, absence of sweating and presence of vasodilatation over the left side of the face and in the left hand. When the right arm was immersed in hot water the temperature of the left middle finger increased. This type of response is similar to that observed in cases 1 and 2 (figs. 1 and 2). The authors stated:

> It should also be noted that a rise in temperature occurred in the finger, the sympathetic fibres to which were presumably interrupted. . . . This constitutes further suggestive evidence for the existence of vasodilator fibres outside the sympathetic nervous system.

The data reported here indicate that the sympathetic fibers are not completely interrupted by a lesion in the lateral medullary area and that this type of experiment, therefore, furnishes no evidence for the existence of vasodilator fibers outside the sympathetic nervous system.

The observations reported here indicate that in man the descending efferent tracts concerned with sweating, with vasoconstriction in response to heating the body and with dilatation of the pupil and retraction of the upper eyelid pass through the lateral medullary area. Although these tracts are mainly uncrossed below the medulla, they probably receive some fibers from the opposite side because the Horner syndrome is not as marked as after peripheral sympathectomy and because vasoconstriction on cooling the body and sweating on heating the body are not completely inhibited. The lack of interference with vasoconstriction caused by sensory stimuli results from a spinal reflex or from more extensive bilateral innervation or because the efferent tracts concerned with this function are anatomically distinct in the medulla from those concerned with sweating or with vasoconstriction in response to body cooling.

Magoun [10] summarized the experimental data on the descending tracts of the autonomic system as follows:

> From a series of recent studies on the brain stem of the cat the conclusion may be drawn that a pathway which descends either directly or through relays to preganglionic sympathetic neurons in the spinal cord arises from the hypothalamus and emerges from the lateral hypothalamic area to pass backward in both the central and tegmental portions of the midbrain. At the pontile level, a concentration of connections in the tegmental region of the brain stem occurs, and in the

9. Duthie, J. J. R., and Mackay, R. M. I.: Vasomotor Reflexes in the Control of Body Temperature in Man, Brain **63**:295 (Dec.) 1940.

10. Magoun, H. W.: Descending Connections from the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:270, 1940.

medulla the pathway is distributed chiefly in the lateral portion of the reticular formation. From the medulla, it descends in the antero-lateral funiculus of the upper cervical cord. This pathway is made up of both ipsilateral and crossed connections, with crossing occurring both in the brain stem and at spinal levels.

He further stated that in cats the different sympathetic effectors are not activated to the same degree by stimulation of a small region along the descending pathway from the hypothalamus.

The study of these 6 patients suggests that the efferent tracts concerned with various functions of the autonomic nervous system are at least in part anatomically distinct in the medulla, so that a lesion may destroy the tracts concerned with one or more functions of the autonomic system without interfering with the remainder. The following combinations were found: (*a*) ptosis of the eyelid with no other evidence of dysfunction (cases 5 and 6); (*b*) Horner's syndrome with hyphidrosis of the ipsilateral half of the face and trunk and upper extremity (case 3); (*c*) hyphidrosis of the ipsilateral half of the face and upper extremity without any evidence of Horner's syndrome (case 4); (*d*) Horner's syndrome and ipsilateral disturbance of sweating and of vasoconstriction in response to cooling the body (cases 1 and 2). The vasomotor responses to sensory stimuli were normal in all the cases (1, 2, 3 and 5) in which observations were made.

In a study of postural hypotension, two of us (Stead and Ebert[11]) showed that certain sympathetic reflexes, i. e., reflex vasoconstriction in response to a fall in arterial pressure, vasomotor reactions in response to changes in body temperature and sweating, may be selectively affected by lesions which they assumed to be in the central nervous system. They concluded that central lesions of the autonomic nervous system produce signs that are different from those caused by removal of the sympathetic ganglia or nerves, just as lesions in the sensory cortex produce signs that differ from those caused by sectioning of the posterior roots. The data given here support that conclusion.

SUMMARY AND CONCLUSIONS

The cases of 6 patients with lesions of the brain stem due to vascular thrombosis are described. Five of the 6 patients had a more or less typical lateral medullary syndrome due to occlusion of the posterior inferior cerebellar artery. The lesion in the sixth patient was probably due to thrombosis of a lateral branch of the superior cerebellar artery.

In 4 cases there were minimal evidences of Horner's syndrome or sweating disturbances. In the 2 cases reported in detail sweating on heating the body and vasoconstriction on cooling the body were seriously

11. Stead, E. A., Jr., and Ebert, R. V.: Postural Hypotension: A Disease of the Sympathetic Nervous System, Arch. Int. Med. **67**:546 (March) 1941.

disturbed, but vasodilatation on heating the body and vasoconstriction from a full inspiration or from sensory stimuli were normal.

This study indicates that the efferent tracts concerned with various functions of the autonomic nervous system are at least in part anatomically distinct in the medulla, so that a lesion may destroy the tracts concerned with one or more functions of the autonomic system without interfering with the remainder.

Central lesions of the autonomic nervous system produce signs that are different from those caused by the removal of the sympathetic ganglia or nerves, just as lesions in the sensory cortex produce signs that differ from those caused by sectioning a peripheral nerve or the posterior roots.

This investigation was carried out with the technical assistance of Miss Rosamond Piotti.

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DISCUSSION

Dr. James C. White, Boston: I was privileged last summer to see a patient with Professor Ferguson in Manchester, England, and to talk with Professor Learmonth in Edinburgh, both of whom are especially interested in thrombosis of the posterior inferior cerebellar artery. The patient whom I saw in Manchester showed exactly the same situation as has been described here. It is an intriguing thought that if one could specifically cut the sympathetic vasoconstrictor fibers in the medulla one would have the ideal operation for the treatment of Raynaud's disease. Persons subjected to this operation maintain an extreme degree of vasodilatation in the hand, with a far better circulation than is seen in patients after a postganglionic sympathectomy for Raynaud's disease, and even better than is present after a preganglionic sympathectomy. I asked Professor Ferguson if he would try the effect on his patient of giving epinephrine to determine the degree of sensitization to this drug. He was going to do it, but I have not had any report from him yet. Presumably there is a maximum sensitization of smooth muscle to epinephrine and sympathin after degeneration of the postganglionic fibers, much less after degeneration of the preganglionic fibers and very little, or none at all, when the upper neuron is cut in the brain stem or the spinal cord. I have performed several operations in which I made sections laterally in the lower portion of the medulla. I was interested to see whether the patients showed any autonomic disturbance, but they did not. From Magoun's work in Ranson's laboratory, I think one must go nearer the central portion of the medulla in order to interrupt the descending autonomic pathways.

Dr. D. Denny-Brown, Boston: Profuse hyperhidrosis may occur on one side of the face for years without other evidence of damage to the cervical sympathetic fibers, or perhaps with only a mild Horner syndrome. It therefore appears reasonable to me that one function in the sympathetic nervous system should be subject to isolated disorder.

DR. JOHN ROMANO, Boston: The first patient who was presented did not have the classic symptoms of thrombosis of the posterior inferior cerebellar artery. The signs consisted of ipsilateral sympathetic and cerebellar dysfunction, contralateral loss of pain and temperature function in the trunk, arm and leg and some evidences of involvement of the posterior column and pyramidal tract. Although she had pain in the left (ipsilateral) eye, there was no objective evidence of a lesion in the descending tract of the nucleus of the fifth nerve. We interpreted the lesion to be thrombosis of a branch of the left superior cerebellar artery or of an atypical branch of the left posterior inferior cerebellar artery.

This somewhat anomalous condition led us to speculate as to the anatomic site of the sympathetic pathways, as we had not seen such extensive involvement of sympathetic function in 4 other patients who had typical lateral lesions of the medulla eight, seven, four and one year, respectively, before they were studied.

However, study of the second patient presented tonight, who had a typical lateral lesion of the medulla, indicates an equal degree of sympathetic involvement. It is probable that the incidence and degree of sympathetic involvement with these lesions have not been noted.

STUDIES ON THE CORPUS CALLOSUM

V. HOMONYMOUS DEFECTS FOR COLOR, OBJECT AND LETTER RECOGNITION (HOMONYMOUS HEMIAMBLYOPIA) BEFORE AND AFTER SECTION OF THE CORPUS CALLOSUM

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The study of absolute defects of the visual fields, such as the homonymous hemianopias, has long engaged the attention of investigators. However, those partial homonymous defects called hemiachromatopsia (color blindness in one-half the visual field) and hemiamblyopia (impairment of visual power in one-half the visual field) have been studied infrequently and for the most part inadequately. In the routine preoperative study of 24 epileptic patients in whom the corpus callosum was surgically sectioned by Dr. W. P. Van Wagenen (Van Wagenen and Herren [1]), 3 were found for whom the results of routine perimetric studies were normal but who showed a disturbance in the recognition of colors, objects and letters in one homonymous field. The present paper deals with the cases of these 3 patients.

The present study is reported for two reasons. It is concerned, first, with the possible value of such a defect in the diagnosis of focal lesions of the brain and, second, with the effects which may occur in the defective homonymous field after the corpus callosum is sectioned. In a previous paper [2] temporary exaggeration of preoperative dyspraxia (case 3 of the present paper) occurred after section of the corpus callosum. Since unilateral motor disturbances may be aggravated, it was of interest to see whether the visual defects would also be affected after section of the corpus callosum.

This study was aided by grants furnished by the Ernest L. Woodward Fund and the John and Mary Markle Foundation.

From the Department of Medicine, Division of Psychiatry, University of Rochester School of Medicine and Dentistry, and the Clinics of the Strong Memorial and Rochester Municipal Hospitals.

1. Van Wagenen, W. P., and Herren, R. Y.: Surgical Division of Commissural Pathways in the Corpus Callosum: Relation to Spread of an Epileptic Attack, Arch. Neurol. & Psychiat. **44**:740 (Oct.) 1940.

2. Akelaitis, A. J.; Risteen, W. A.; Herren, R. Y., and Van Wagenen, W. P.: Studies on the Corpus Callosum: III. Contribution to the Study of Dyspraxia and Apraxia Following Partial and Complete Section of the Corpus Callosum, Arch. Neurol. & Psychiat. **47**:971 (June) 1942.

METHOD AND PROCEDURE

Studies were carried out on a Ferree-Rand type of perimeter by Drs. Dewey D. Yoder, Wesley F. Bosworth and Charles L. Block. In all 3 patients the visual fields as tested to a 5 mm. white object were normally full or bilaterally equal before and after operation.

The same tests were performed before and at frequent intervals after operation. Absolute orientation and recognition of colors, objects and letters were tested in the manner described in a previous paper.[3] In view of the presence of object agnosia in the hemiamblyopic field, relative orientation and appreciation of absolute and relative size required modified test objects. These patients could distinguish between dull and bright and white and black objects.

The homonymous field of each eye was tested separately. Attempts to map out the fields for recognition of colors, objects and letters were carried out by means of a Bjerrum screen for each patient, but the results were contradictory so often that their value was questionable. The patients invariably looked toward the object in the defective field. Gross studies were found much more reliable and did not tax the subject's patience too much. Epileptic persons are apt to become irritable and uncooperative if tests are too detailed. The studies were made in an office well illuminated by daylight. Additional studies included the determination of the degree of illumination appreciation in each homonymous field of each patient before and after operation. The method of flashing a light at identical points in each homonymous field is a subjective test and not very reliable. A far better method is testing the subject's appreciation of various shades of gray as utilized in fifty shades of Hering's gray paper series. Each card consists of a white paper 6 by 8 cm. on which an area of a shade of gray measuring 2 by 5 cm. is superimposed at one corner. Cards were exposed in each homonymous field, and the patient was then requested to match the shade with the samples before him in direct gaze. Various combinations of two shades of gray were presented simultaneously in each homonymous field, and the patient was required to designate which rectangle of gray was lighter or darker in hue.

Appreciation of form was studied in each homonymous field by the use of various geometric figures as found in year 4, test 2 for discrimination of forms in the Stanford-Binet series.[4] The form was shown in the homonymous field, and the patient was requested to name or point to the form on a sample card in direct gaze.

The suggestion made by Oppenheim [5] of testing the patient's attentiveness to objects in each homonymous field was employed. In this test two similar objects are exposed simultaneously at identical points in each homonymous field, and the patient may fail completely to appreciate the one which falls in the defective half-field. However, he sees the object as something which he cannot name if the examiner exposes the object alone in the same position in the defective homonymous field.

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3. Akelaitis, A. J.: Studies on the Corpus Callosum: II. The Higher Visual Functions in Each Homonymous Field Following Complete Section of the Corpus Callosum, Arch. Neurol. & Psychiat. **45**:788 (May) 1941.

4. Terman, L. M.: The Measurement of Intelligence, Boston, Houghton Mifflin Company, 1916, p. 152.

5. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 1113.

Pathoanatomic studies were not made. However, clinical and roentgenologic studies showed evidence of lesions in the posterior portions of the cerebral hemispheres. Electroencephalographic studies were made by Dr. John B. Hursh, of the department of physiology.

REPORT OF CASES [6]

CASE 1 (case 10 [2]).—E. K., a white single woman aged 30, was admitted to the Rochester Municipal Hospital, Nov. 6, 1939. At the age of 15 she suffered a head injury in an automobile accident but showed no disturbance of consciousness. Two years later, at the age of 17, grand mal seizures developed. Generally they occurred just after or just before falling asleep. She would be aware of an aura of numbness in her left arm and cry out and lose consciousness. Clonic and tonic movements would begin on the left side and subsequently involve the entire body. Early in the course of her illness the attack could be aborted by vigorous massage of the left arm, but in recent years this had proved ineffective.

Examination.—The patient was garrulous, misanthropic and irritable, with a Binet level of 14 years. A rough systolic murmur heard over the precordium suggested mitral insufficiency. The neurologic status revealed questionable atrophy of the left arm, and she was not as skilful in using this arm for ordinary tasks as one would normally expect. Reflexes and sensation were intact. The cranial nerves, except for the visual apparatus, were normal.

The pupils were centric and equal and reacted to light and in accommodation. Examination of the fundi revealed no abnormalities. Vision was 6/7.5 in the right eye and 6/6 in the left eye.

The visual fields were full as studied with a 5 mm. white object in the perimeter. The patient showed no difficulty in the recognition of colors, objects or letters in the right homonymous field but was unable to recognize them in the left. She presented no difficulty in absolute or relative orientation or in appreciation of absolute and relative size. Appreciation of shades of gray was impaired in the left field—usually she guessed the shade as being lighter. She appreciated flashes of light less vividly in the left homonymous field. Attentiveness in the left half-field was impaired, as revealed in the Oppenheim test. Whereas forms were all identified correctly in the right homonymous field, they were completely misidentified in the left half-field.

Laterality studies revealed left eyedness, right handedness and right footedness.

Laboratory Studies.—Stereograms with the head in the anteroposterior position revealed calcification and displacement of the pineal gland to the right. A ventriculogram showed marked dilatation of the temporal and occipital horns, as well as the posterior end of the body of the ventricle on the right side. This was interpreted as evidence of a scar in the right temporo-occipital region. Electroencephalograms revealed short outbursts of delta waves (4 to 6 per second) over the entire scalp, but they were of greatest amplitude over the right parieto-occipitotemporal region.

Operation.—On November 20 a right frontoparietal craniotomy was performed and the corpus callosum was completely sectioned. Two large veins entering the longitudinal sinus from the right frontal lobe had to be ligated to allow retraction.

Course.—During the first two weeks after operation the patient remained in a peculiar mute state. She would cooperate to spoken requests and write answers to questions asked her. At times she assumed mildly cataleptoid states, and frequently her actions were of the slow motion type seen in the cinema. She showed

6. These cases have been reported in greater detail as regards voluntary activity in a previous paper.[2] The case number in parentheses will identify the case.

no dyspraxia, astereognosis or dysgraphia in either hand. She slowly became more responsive, and tests on December 9 and subsequently showed normal activity.

The visual functions were tested for the first time after operation on December 13. Perimetric examination revealed that the visual fields were full. Orientation and recognition of size were intact in the left half-field. Red, white and dark blue were appreciated correctly in the left half-field, but light blue, green and yellow were identified as yellow, blue and white, respectively. The patient recognized a pencil correctly in the left half-field but misidentified ten other objects. Her usual response was "I see it but don't know what it is." She was unable to recognize letters in the left field. These tests were repeated several times, with the same results. The following day she recognized red correctly and orange appeared red, but other colors were misidentified. Subsequent examinations revealed usually loss of color recognition in the left half-field. Tests for acuity of illumination perception by means of flashes of light and Hering's shades of gray suggested that there was impairment in the left visual field as compared with the right. Appreciation of form was absent and attentiveness was impaired in the left field.

The patient was discharged on Jan. 22, 1940. She has been examined on many occasions, the last study being made in August 1941. The changes have been essentially the same as those previously described.

The nature of the seizures has changed. Since operation they have consisted of an aura of numbness on the left side of her face and left arm, followed by tonic and clonic movements of the left side, but she remains conscious throughout the attack. After the seizure her left side is paralyzed for a variable length of time.

CASE 2 (case 9[2]).—F. O'B., a white married man aged 27, was admitted to the Strong Memorial Hospital, Oct. 11, 1939. At the age of 12 he fell from a railroad car, striking his head on the tracks, and was rendered unconscious. Grand mal seizures developed one year later and continued to occur. During the past four years he had had postconvulsive states of excitement with amnesia and severe attacks of rage (psychomotor fits [?]), in which his gait was normally steady. In the latter attacks he had torn off his wife's clothes and "raped" her. Usually he had enough recollection of these rage attacks to become depressed afterward. In the last few years he had become a periodic drinker. Incidentally, the rage attacks were not related to his alcoholic sprees.

Examination.—The patient was irritable and hostile, with a Binet level of 13 years 8 months. His physical condition was good. The neurologic status was normal except for left homonymous hemiamblyopia.

The pupils reacted to light and in accommodation, and the fundi were normal. Vision was 6/10 in each eye.

The visual fields as studied with a 5 mm. white object in the perimeter revealed slight but equal contraction bilaterally. The right homonymous field presented no disturbance, while the left homonymous field showed complete inability to recognize objects and letters. He usually appreciated white, yellow and black in the left half-field, but other colors were interpreted as gray. All colors appeared light in hue in the periphery and became darker as the midline was approached. It should be emphasized that those colors which he recognized correctly were appreciated in the field well beyond the limits of the macular zone (varying from 2 to 10 degrees around the point of fixation). He showed diminution in acuity of perception of illumination in the left homonymous field. Flashes of light appeared brighter in the right field than at identical points in the left field, and his appreciation of the individual shades of gray was slightly impaired in the left field. In the discrimination of two shades of gray shown simultaneously in the left homonymous field the incidence of errors was 40 per cent, as against

10 per cent in the right field. Appreciation of absolute size was disturbed in the left field, objects appearing half as large in this field as they did in the opposite field. Relative size was appreciated adequately. Absolute orientation was disturbed; he invariably pointed to the left and anteriorly. Relative orientation was good in both fields. Appreciation of form was lost in the left homonymous field. Attentiveness as evaluated by the Oppenheim test was impaired in the left half-field.

Laterality studies revealed left ocular dominance. He was right footed in various tests. Handedness was mixed; he had always written with his left hand, but many unimanual tasks requiring strength were performed with his right hand.

Laboratory Studies.—An encephalogram revealed asymmetry in the size of the ventricles, the right being larger than the left. The anterior portions of the ventricles were shifted to the left, but the posterior portions were in normal position. Electroencephalographic studies revealed short (three to fifty seconds) bursts of delta waves, mainly over the right temporoparieto-occipital and the left parietal region, which were not accompanied by subjective symptoms. Dr. J. B. Hursh interpreted these findings as suggestive of multiple foci of disturbance. On one occasion, shortly after a grand mal seizure, delta waves (2 per second) were found in the frontal leads and large (500 microvolts) spikes were obtained from the left parietal region.

Operation.—On November 3 a right frontoparietal craniotomy was performed and the corpus callosum was completely sectioned.

Course.—The patient was hostile in his attitude for the first ten days after operation and appeared mildly confused, especially at night. Subsequently it was discovered that he had almost complete amnesia for this period. He could recall, however, that during this time his hands felt strange. He thought that some one was holding his left hand, only to discover that he was actually grasping his own hands. At other times when clasping his hands he had the sensation that an inanimate object was between them. The neurologic status remained the same as before operation.

The visual fields were studied in detail on November 14 for the first time after operation. To gross tests the visual fields appeared full. Agnosia and alexia persisted in the left homonymous field. The disturbance in recognition of colors and their other defects were of the same nature as before operation.

The patient was examined in detail on two successive days before his discharge on Nov. 22, 1939. The same results were obtained except that he showed better ability to recognize colors in the left half-field.

Subsequent Course.—Since his discharge he has been studied on numerous occasions in the hospital up to November 1940 because of an infected bone flap. He has never shown signs of meningitis, and the bone flap has been removed. Perimetric examination on Dec. 12, 1939 showed slightly contracted fields, similar to those observed preoperatively. On occasion he recognized an object correctly in the left visual field, but I believe that this was by chance. Color recognition in the left field was sometimes found to be good for all except green, but was apt to fluctuate from one examination to the next. It is probable that fatigue increased the hemiachromatopsia, and repetition of tests improved recognition. Frequently he commented on the fact that the different colors possessed different shades in the left field.

Case 3 (case 14[2]).—M. L. P., a white girl aged 10 years, was admitted to the Strong Memorial Hospital, March 12, 1940. The psychobiologic development was normal to the age of 3 years, when she walked and talked satisfactorily. At this time she was struck over the left parietal region by a falling object. Two weeks later status epilepticus, of five hours' duration, developed. After she

regained consciousness, the family noticed aphasia, paralysis of the right side of the body and external strabismus. The strabismus improved at the end of three weeks, and she began to talk after two months. The paralysis improved gradually, so that at the time of admission her gait was only slightly spastic and she showed merely a slight clumsiness in her right hand. She remained free of seizures until six months ago, prior to admission, when she began to have petit mal seizures. During this time she has become irritable and is apt to tire easily.

Examination.—The patient was an attractive, rather silly girl, with a Binet level of 9 years 9 months and an intelligence quotient of 92. The physical status was not remarkable except for the neurologic findings. She showed the residua of right hemiplegia, with increased motor tonus, exaggerated deep reflexes and an extensor response of the big toe on the right side to plantar stimulation. Sensation, including two point discrimination, stereognosis and tactile lexia, was intact in each hand. Except for a slight amount of ataxia in the right hand, she was able to perform various tasks surprisingly well but could not shuffle cards. She was able to write with either hand.

The cranial nerves were intact except for the oculomotor system and the visual fields. She had left external strabismus. She was unable to converge with both eyes open, but with either eye closed the other eye came in normally as it followed an object in. Pupils reacted to light and in accommodation. The fundi were normal. She could not read with her left eye; vision was 3/60 in this eye and 6/6 in the right eye.

The visual fields as studied with a 5 mm. white object in the perimeter were slightly but equally contracted. The left homonymous field showed no defects. In the right homonymous field she was unable to recognize colors, objects or letters. Orientation (absolute and relative) and estimation of size (absolute and relative) were not disturbed. Appreciation of form was lost in this field and attentiveness as elicited by the Oppenheim test was impaired. Acuity of illumination perception was disturbed in this field; she tended to interpret various shades of gray as much lighter, and flashes of light were appreciated as less bright than in the left homonymous field.

Laterality studies disclosed right ocular dominance, left handedness and left footedness.

Laboratory Studies.—Encephalograms revealed dilatation of the left lateral ventricle, particularly of its posterior portion, with shifting of all ventricular structures to the left. Several electroencephalograms taken at various times showed 6 per second delta waves with an amplitude of 15 to 20 microvolts over the left parietal region and infrequent delta waves of less than 10 microvolts in the right upper frontal and in both temporocentral leads. Dr. Hursh interpreted these findings as indicating a focus in the left parietal region and questionable subsidiary foci in those areas described as showing delta waves of very low amplitude.

Operation.—On March 29 a right frontoparietal craniotomy was performed and the corpus callosum sectioned almost completely except for the posterior 0.5 cm of the splenium. The left fornix was divided.

Course.—For one month the patient showed perseveration in tasks and conversation, with irregular forced innervation in the right hand. Although she could write with her right hand five days after operation and sensory studies were normal, astereognosis was present in this hand.

Visual studies were first made on April 18, and the results were identical with those obtained preoperatively. She was reexamined on May 1 and 10, with

the same results. Since her discharge on May 18 she has been studied in detail in November 1940 and October 1941. The status of the right homonymous field has continued the same as before operation.

Summary of Pertinent Observations in Three Cases of Homonymous Hemiamblyopia

	Case 1. E. K. Relation of Tests to Operation		Case 2. F. O'B. Relation of Tests to Operation		Case 3. M. L. P. Relation of Tests to Operation	
	Before	After	Before	After	Before	After
Visual functions						
Perimetric fields	Full	Full	Slightly contracted bilaterally	Slightly contracted bilaterally	Slightly contracted bilaterally	Slightly contracted bilaterally
Homonymous field defect	Left	Left	Left	Left	Right	Right
Illumination appreciation						
Light	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired
Hering test	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired
Attention	Impaired	Impaired	Impaired	Impaired	Impaired	Impaired
Orientation						
Absolute	Normal	Normal	Normal	Normal	Normal	Normal
Relative	Normal	Normal	Impaired	Impaired	Normal	Normal
Size						
Absolute	Normal	Normal	Normal	Normal	Normal	Normal
Relative	Normal	Normal	Impaired	Impaired	Normal	Normal
Form	Lost	Lost	Lost	Lost	Lost	Lost
Color	Lost	Lost	Partly lost	Partly lost	Lost	Lost
Objects	Lost	Lost	Lost	Lost	Lost	Lost
Letters	Lost	Lost	Lost	Lost	Lost	Lost
Other neurologic changes	Slight atrophy of left arm (?)	Slight atrophy of left arm (?)	None	None	Residual right hemiplegia; left external strabismus; L. E., 3/60	Residual right hemiplegia; left external strabismus; L. E., 3/60; astereognosis in right hand
Lesion	Scar in right temporo-occipital region		Right lateral ventricle dilated		Left lateral ventricle dilated	
Operation	11/20/39: Complete section; right craniotomy		11/3/39: Complete section; right craniotomy		3/29/40: Almost complete section (last 0.5 cm. splenium not cut); left fornix divided; right craniotomy	
Laterality* studies	L. E., R. H., R. F.		L. E., L./R. H., R. F.		R. E., L. H., L. F.	

* L. E. indicates left ocular dominance; R. E., right ocular dominance; L. H., left handedness; R. H., right handedness; L./R. H., ambidexterity; L. F., left footedness, and R. F., right footedness.

COMMENT

From a perusal of the observations, as summarized in the accompanying table, it is obvious that complete (cases 1 and 2) and partial

(case 3) section of the corpus callosum produced no accentuation of or addition to the defects in the homonymous visual fields present before operation.

In a discussion of the signs encountered those common to each patient should be mentioned first. Thus, in each patient loss of recognition of forms, objects and letters and impairment of attentiveness and of perception of illumination were present. The inability to recognize forms, letters and objects was probably due to poor perception. The usual remark was "I see something is there, but I can't tell you what it is." The object appeared vague and "misty like" and seemed to have no depth. Occasionally the subject identified the object as something "shiny" or "dull" but never saw it in sufficiently sharp outline to allow positive identification. The difficulty was not diminished by increasing the size of the object. According to Lissauer,[7] one would say that apperception (the act of conscious perception of a sensory impression) was impaired. Hemiachromatopsia was observed in 2 cases (1 and 3). In case 2 there was partial hemiachromatopsia; the patient usually appreciated white, yellow and black correctly, and occasionally light blue and orange. Red and dark blue were often called orange and blue or green, respectively. It is common knowledge that colors tend to be lighter in hue as one approaches the periphery of the field (Baird[8]). It appears likely, therefore, that the patient tended to show that sort of visual efficiency near the line of direct vision which he showed only in the distal portions of the homonymous visual field on the normal, or right, side. These changes in case 2 associated with impairment of perception of illumination and those in cases 1 and 3 tend to substantiate the observations of Merle,[9] Magitot and Hartmann,[10] Brouwer,[11] Bender and Kanzer[12] and others that impairment of color vision in homonymous fields is associated with disturbances of visual acuity. This lends support to a unitary conception of these hemiamblyopias, namely, that they are a result of an early or partial involvement of the primary visual pathways.

7. Lissauer, H.: Ein Fall von Seelenblindheit nebst einem Beitrag zur Theorie derselben, Arch. f. Psychiat. **21**:222, 1889.

8. Baird, J. W.: The Color Sensitivity of the Peripheral Retina, Publication 29, Carnegie Institution of Washington, 1905.

9. Merle, P.: Aphasie et hémiachromatopsie, Rev. neurol. **16**:1129, 1908.

10. Magitot, A., and Hartmann, E.: La cécité corticale, Bull. Soc. d'opht. de Paris, 1926, p. 427; A propos des cécités corticales et sous-corticales, ibid., 1926, p. 639.

11. Brouwer, B.: Erkrankungen der Sehstrahlung und der Sehrinde, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6, p. 505.

12. Bender, M. B., and Kanzer, M. G.: Dynamics of Homonymous Hemianopias and Preservation of Central Vision, Brain **62**:404, 1939.

Other observations also lend support to this concept. In each patient the fields were of equal extent in the two eyes as found by perimetric tests. However, patients 1 and 2 admitted that the small white object was appreciated more vaguely in the periphery of the defective field than in the periphery of the opposite field. Similarly, movement, although appreciated, was not perceived as vividly in the defective as in the normal field. In other words, the sensory impairment extended even to the most primitive aspects of vision.

The results of the study of visual fields in cases of brain tumor and cerebral hemorrhage lend support to the belief that hemichromatopsia and hemiamblyopia are incomplete forms of hemianopia, as a review of the published cases by Wilbrand and Sänger [13] suggests. Recently, Bender and Kanzer [12] studied this relationship in detail. One interesting aspect of the hemiachromatopsia in cases 1 and 3 was the patients' comment that the colors appeared to be various shades of gray. In the cases reported by Ziel,[14] Axenfeld [15] (case 6), Bjerrum,[16] Uhthoff [17] (case 8 [17a]) and Samelsohn [18] all colors appeared gray in the hemiachromatopsic field. Even patient 2 remarked spontaneously that the colors possessed a bluish haze, and even those colors which he recognized correctly in the periphery of the left homonymous field appeared more vivid in direct gaze or in the right homonymous field.

Of the remaining signs, absolute and relative orientation and appreciation of absolute and relative size were not disturbed in either homonymous field in cases 1 and 3. In case 2 absolute orientation and perception of absolute size were definitely disturbed in the hemiamblyopic field, while relative orientation and relative differentiation of size were intact. The size of an object in the left field appeared half as large as in the right, or normal, field. The patient invariably pointed to the left and anteriorly to objects in the left homonymous field. This dissociation is

13. Wilbrand, H., and Sänger, A.: Die Erkrankungen der Sehbahn vom Tractus bis in den Cortex, in Die Neurologie des Auges, Wiesbaden, J. F. Bergmann, 1917, vol. 7, p. 26.

14. Ziel: Verhandl. d. Gesellsch. deutsch. Naturf. u. Aertze **67** (pt. 2):184, 1895; cited by Wilbrand and Sänger.[13]

15. Axenfeld, T.: Hemianopische Gesichtsfeldstörungen nach Schädelschüssen, Klin Monatsbl. f. Augenh. **55**:126, 1915.

16. Bjerrum, J.: Hemianopsia for Colors, Hospitalstid. **8**:41, 1881; cited by Wilbrand and Sänger.[13]

17. Uhthoff, W.: (*a*) Beiträge zu den hemianopischen Gesichtsfeldstörungen nach Schädelschüssen, besonders solchen im Bereich des Hinterhauptes, Klin. Monatsbl. f. Augenh. **55**:104, 1915; (*b*) Ein Beitrag zu den Sehstörungen bei Zwergwuchs und Riesenwuchs resp. Akromegalie, Berl. klin. Wchnschr. **34**:537, 1897.

18. Samelsohn, J.: Zur Frage des Farbensinncentrums, Centralbl. f. med. Wissensch. **19**:850 and 900, 1881.

all the more interesting in view of the fact that in this case certain colors were appreciated in the defective field while complete hemiachromatopsia existed in cases 1 and 3. I cannot explain these results adequately and mention them merely as facts. It is possible that in case 2 severe damage to the supramarginal and angular gyri may have been present to account for the spatial disorientation. Riddoch [19] found that spatial disorientation may occur in homonymous half-fields alone as a result of unilateral lesions of the parietal lobe. The interesting fact that the patient in case 1 was able to point correctly and effectively to objects in the defective visual field with the hand innervated by the contralateral hemisphere even after complete section of the corpus callosum strongly suggests the possibility that interhemispheral commissural pathways other than the corpus callosum can be utilized in this type of activity.

The findings in this series of 3 cases of hemiamblyopia suggest that there is a concomitant relationship between visual acuity and recognition of forms, colors, objects and letters and attentiveness. In other words, one is dealing with degrees of visual imperception. This study does not lend support to Poppelreuter's [20] concept of the six stages in the disintegration of visual functions, since even perception of movement was disturbed in the defective homonymous fields of these patients.

Stereoscopic vision was lost preoperatively in case 3. In case 1 the patient insisted that it was "foolish to expect to see yellow from red and green." It was impossible to dissuade her from her preconceived idea. In case 2 there was no difficulty with stereoscopic vision before and after operation.

Localization Value of Homonymous Hemiamblyopia.—All 3 patients gave a history of head trauma. In case 1 a sensory aura suggestive of the onset of the convulsion in the right parietal lobe was present. The interesting jacksonian seizures following operation suggest the march of the seizure from the right parietal to the right frontal cortex. Ventriculograms disclosed marked dilatation of the temporal and occipital horns, as well as of the posterior end of the body of the right ventricle. Electroencephalograms revealed delta waves of greatest amplitude over the right parieto-occipitotemporal region. All of these findings serve as evidence of a lesion in the right parieto-occipitotemporal region, and it is probable that such a lesion produced the left hemiamblyopia.

In case 2 the dilatation of the right ventricle and the bursts of delta waves over the right temporo-parieto-occipital region pointed to a lesion in this area which probably caused the left hemiamblyopia.

19. Riddoch, G.: Visual Disorientation in Homonymous Half-Fields, Brain **58**:376, 1935.

20. Poppelreuter, W.: Zur Psychologie und Pathologie der optischen Wahrnehmung, Ztschr. f. d. ges. Neurol. u. Psychiat. **83**:26, 1923.

In case 3 the history of aphasia and the occurrence of right hemiplegia at the age of 3 suggested an extensive injury to the left cerebral hemisphere. The neurologic status confirmed this. Encephalograms disclosed hydrocephalus involving the left lateral ventricle, especially its posterior portion. Electroencephalographic studies revealed a focus of abnormal discharge over the left parietal region. These findings indicated that in all probability the right hemiamblyopia was a result of a lesion in the left hemisphere.

In brief, therefore, the evidence in each of the 3 cases suggests that the hemiamblyopia resulted from a lesion in the posterior portion of the contralateral hemisphere. Case 2 is especially significant in view of the fact that the hemiamblyopia was the only clinical sign in an otherwise normal neurologic examination. It would seem advisable, therefore, to study the higher visual functions in each homonymous field, even though the visual fields as studied with a perimeter are full or bilaterally equal in extent.

In the literature on cases of hemiachromatopsia with pathoanatomic studies almost all the investigations disclosed lesions in the hemispheres (Wechsler [21]). However, a lesion of the optic tract may produce hemiachromatopsia, as seen in the case of Uhthoff.[17b] Whether the Wernicke pupillary phenomenon could be utilized in cases of hemiamblyopia to distinguish between an infrageniculate and a suprageniculate lesion is doubtful. In the 3 cases reported here the Wernicke phenomenon was normal in each homonymous field. However, inasmuch as light perception persisted in the defective field in Uhthoff's case, the Wernicke pupillary phenomenon was found to be normal in the defective field. Accordingly, hemiamblyopia has only limited localization value. At present it can be utilized only as evidence of a lesion in the optic system posterior to the optic chiasm.

SUMMARY AND CONCLUSIONS

Three cases of homonymous hemiamblyopia in epileptic patients with a history of head trauma are reported. In 1 case the hemiamblyopia was the only neurologic sign observed.

The localizing value of this type of homonymous defect is analyzed and found to be limited.

Complete or partial section of the corpus callosum produces no changes in the hemiamblyopic visual field.

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21. Wechsler, I. S.: Partial Cortical Blindness with Preservation of Color Vision, Arch. Ophth. **9**:957 (June) 1933.

Case Reports

DIABETES INSIPIDUS AND OTHER UNUSUAL COMPLICATIONS OF ACUTE PURULENT SINUSITIS

Clinicopathologic Study of a Case

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Philadelphia

The neurologic complications of infection of the paranasal sinuses are numerous and include pachymeningitis externa and extradural abscess, pachymeningitis interna and subdural abscess, circumscribed leptomeningitis, protective meningitis, bacterial meningitis, brain abscess, nonsuppurative encephalitis, thrombophlebitis of the intracranial venous channels and involvement of many cranial nerves. These complications present frequently perplexing diagnostic and therapeutic problems, defying the combined efforts of the otorhinologist, the ophthalmologist and the neurologist. The reasons for these difficulties have been discussed previously by one of us (Yaskin [1]). In the case to be discussed in this paper there occurred, in addition to the rather common basilar meningitis, the unusual complications of osteomyelitis of the lesser wing of the sphenoid bone, rapidly progressive optic neuritis, partial thrombotic occlusion of one of the middle cerebral arteries, changes in the hypothalamus and transient diabetes insipidus. In addition, the type of cortical destruction produced by occlusion of the middle cerebral artery afforded the opportunity to reconsider the problem of the so-called functional end arteries of the cerebral cortex.

REPORT OF CASE

In a 21 year old man bilateral optic neuritis developed after diving, and within three weeks subarachnoid bleeding, left hemiplegia and hemianesthesia, meningitis, diabetes insipidus and terminal generalized convulsions occurred. Necropsy disclosed purulent osteitis of the sphenoid bone, basilar meningitis and lesions in the hypothalamic nuclei, thrombotic occlusion of the right middle cerebral artery and incomplete softening of the corresponding area of the cerebral cortex.

History.—J. M., aged 21, a student, was admitted to the Graduate Hospital, in the service of Dr. George M. Coates, on Aug. 30, 1939, complaining of failing vision in both eyes. The family and the past medical history were irrelevant. He was an athlete and was considered a good swimmer. During the few months prior to his admission to the hospital he had had a discharge from the nose, which was regarded as rose fever. About three weeks antedating admission, after swimming and diving, there developed severe generalized headache and impairment of vision in the right eye. Subsequently vision became greatly impaired in the right eye

Read before the Philadelphia Neurological Society, Nov. 28, 1941.

From the Graduate Hospital and the Laboratory of the Neurosurgical Department of the University of Pennsylvania.

1. Yaskin, J. C.: Neurologic Complications of Infections of Temporal Bone and Paranasal Sinuses, Arch. Otolaryng. **30**:157 (Aug.); 360 (Sept.) 1939.

and somewhat impaired in the left eye. Prior to his admission to the hospital a diagnosis of pansinusitis was made and he was subjected to a submucous resection and other procedures for drainage. His headache disappeared, but his sight became progressively worse, especially in the right eye.

General Examination.—On admission to the Graduate Hospital his temperature was 98.2 F. and his pulse rate 100 per minute. The results of the general somatic and neurologic examinations were normal. Urinalysis and blood counts revealed nothing abnormal.

He was immediately seen by Dr. Luther Peter, who made a diagnosis of retrobulbar neuritis in both eyes, especially the right. Visual acuity in the right eye was decreased to light perception at 1 foot (30.5 cm.) and in the left eye to 6/15 + 2. Ophthalmoscopic tests showed bilateral neuroretinitis, with congestion of the veins.

On August 31 Dr. Coates, after cleaning out the right ethmoid cells, probed the sphenoid sinus. It was found to contain a considerable quantity of pus. In entering the sinus the sphenopalatine artery was unavoidably injured. The resulting hemorrhage was controlled by packing. While this was done the patient experienced a generalized convulsion of one minute's duration. An hour later, in his room, it was discovered that his left arm and leg were paralyzed.

First Neurologic Examination.—On August 31, about an hour after the operation, the patient appeared pale, with some swelling of his eyelids. He was restless, uncooperative and somewhat delirious. Nuchal rigidity and the Kernig sign were not present. The fundi could not be satisfactorily visualized. No extraocular palsies were noted. There were definite palsy of the left side of the face of central type and complete flaccid paralysis of the left arm and leg. The tendon reflexes were within normal limits, and a Babinski sign could be elicited on the right side. There was anesthesia to pinprick over the left side of the body, including the face.

Subsequent Observations.—On September 1 the patient's temperature was 100 F. and the pulse rate 84. He appeared to be rational. He now had rigidity of the neck and a Kernig sign bilaterally. In addition, he had complete left hemiplegia with hemianesthesia for pain, position and vibration sense. A spinal tap on that day revealed a bloody spinal fluid under high pressure.

Dr. Peter reported a total blindness in both eyes.

On September 2 the temperature was 100 F. and the pulse rate 100. Neurologic signs were unchanged. The spinal fluid was under a pressure of 150 mm. of water and was bloody. Culture of material from the right ethmoid cells revealed Staphylococcus aureus haemolyticus. The blood culture was reported to be sterile.

Dr. Peter reported slight drooping of the right upper eyelid.

The fluid intake for the day was 2,680 cc. and the urinary output 1,260 cc.

The patient's condition from September 3 to September 15 may be summarized as follows: The temperature varied between 100 and 101 F. and the pulse rate from 80 to 110. The blood pressure was elevated to 150 systolic and 70 diastolic. Evidence of meningeal irritation continued, and the hemiplegia and hemianesthesia on the left side remained unchanged. On September 4 choking of the disks developed, and within a few days there appeared, in addition, marked pallor of both disks. The red blood cell count dropped markedly. Polyuria and polydipsia developed. His fluid intake exceeded 3,000 cc., and his output ranged from 2,000 to 3,500 cc.

On September 7 slight proptosis of the right eyeball was observed. The spinal fluid was under a pressure of 280 mm. of water and was xanthochromic. Culture of the spinal fluid was negative for organisms.

On September 16 his temperature rose to 103 F.; his pulse rate was 100, and his blood pressure was 150 systolic and 70 diastolic. The meningeal signs increased. A spinal tap showed 1,075 cells per cubic millimeter, with 50 per cent polymorphonuclears. He had a profuse hemorrhage from the nose. His fluid intake was 3,575 cc. and his output 3,170 cc. On September 17 he was seized with a generalized convulsion, after which the temperature was 105 F. and the pulse rate 150. From this time his condition became progressively worse until his death, on September 21.

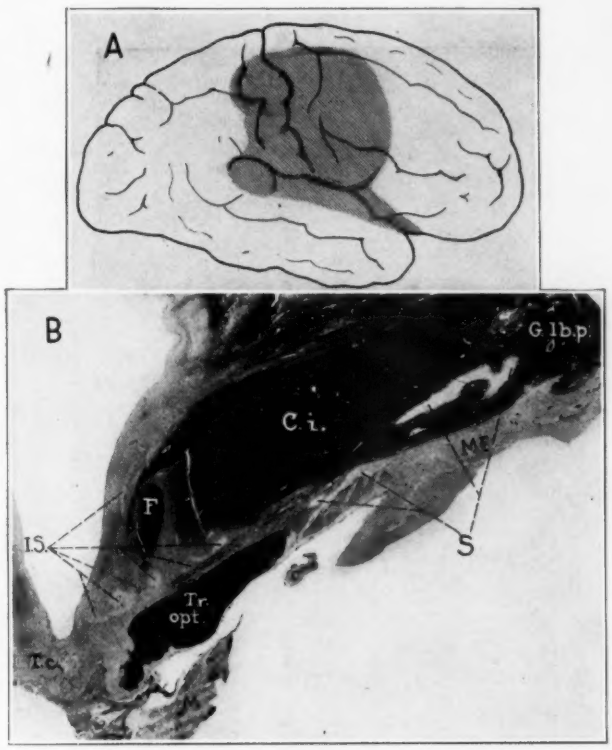

Fig. 1.—*A*, diagram indicating the area of incomplete cortical softening.

B, section through the tuber cinereum (*T. c.*) and the right hypothalamus. *C. i.* indicates internal capsule; *M*, area of meningitis; *F*, fornix; *Glb. p.*, globus pallidus; *ME*, area of meningoencephalitis; *S*, foci of softening; *I. S*, foci of incomplete softening in the hypothalamic nuclei, and *Tr. opt.*, optic tract. Myelin sheath stain; × 3.

Pathoanatomic Diagnosis (Dr. S. C. Muckenbach).—The diagnosis was purulent frontal and sphenoid sinusitis; purulent osteitis and necrosis of the right lesser wing and the sellar walls of the sphenoid bone; purulent mastoiditis, and atelectasis of the lower lobe of the left lung. No thrombus was found anywhere in the body.

Brain.—Gross Examination: The contours were normal. However, the cortex was soft and gray-brown over a wide area of the right hemisphere, extending from the frontotemporal region astride the sylvian fissure to the postcentral sulcus

(fig. 1 *A*). Sections through this area presented a thin cortical lamella, seemingly separated from the underlying white matter.

The leptomeninges of the base of the brain were dense and milky, especially over the chiasmatic cistern. The left optic nerve measured 4 mm. in diameter and the right 3 mm.

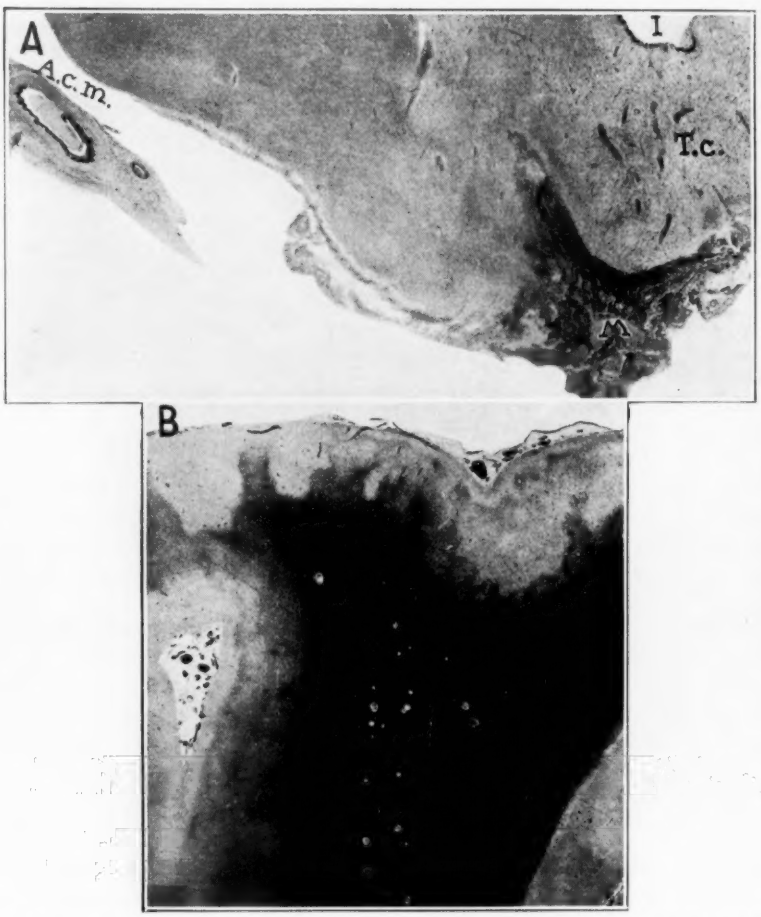

Fig. 2.—*A*, inflammatory infiltration of the infundibulum of the third ventricle (*I*) and the tuber cinereum (*T.c.*) from an area of purulent basal meningitis (*M*). Panarteritis of the right medial cerebral artery (*A. c. m.*), with destruction of the elastic membrane and formation of a marginal thrombus, is present. Weigert's elastica stain; × 15.

B, patchy anoxic changes of the cortex, with loss of myelin fibers in the borderline of the cortical obliteration. Myelin sheath stain; × 7.2.

Microscopic Examination: The left optic nerve showed patchy demyelination. The medulla oblongata, the cerebellum and the midbrain were essentially normal, except for mild swelling of all cellular elements. The leptomeninges about the

tuber cinereum of the diencephalon were heavily infiltrated with polymorphonuclear leukocytes and lymphocytes. The inflammatory process involved the basilar blood vessels and invaded the floor of the third ventricle, as well as the lateral hypothalamic region (fig. 1*B*). The right middle cerebral artery showed irregular, spotty infiltration of its walls and at one point a well organized thrombus, partially occluding the lumen (fig. 2*A*). Multiple areas of incomplete and complete softening were observed in the medial and inferior portions of the right globus pallidus and its neighborhood (fig. 1*B*). The nerve cells of both supraoptic nuclei were swollen, and the supraopticohypophysial and tuberohypophysial tracts, as well as the right optic tract, were severely demyelinated.

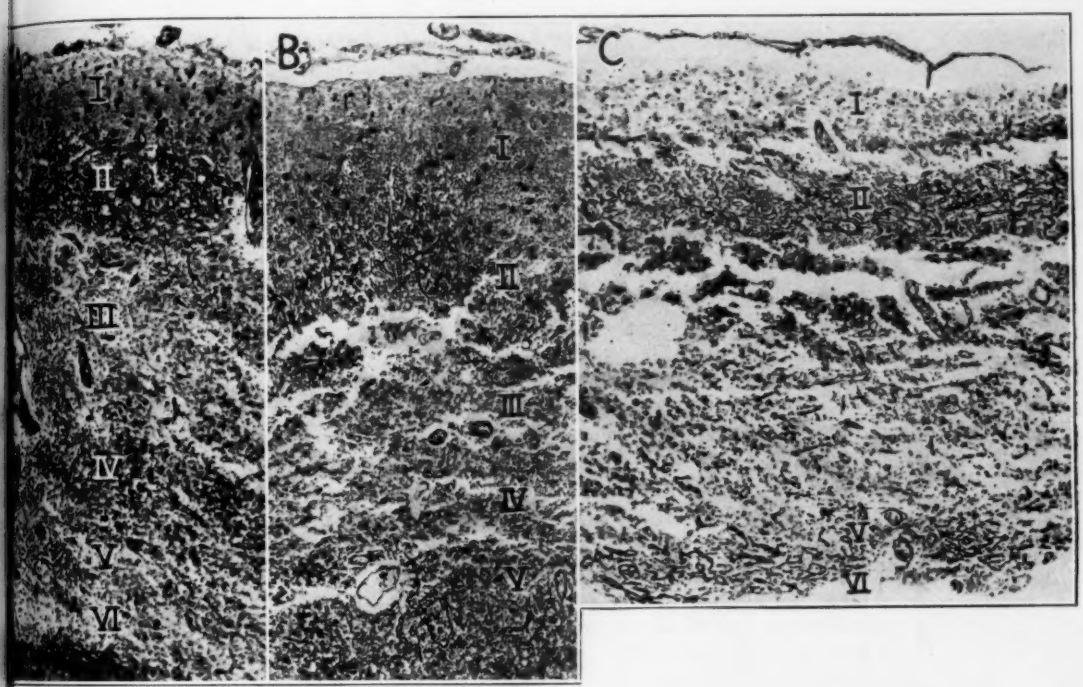

Fig. 3.—Three stages of anoxic cortical necrosis. The molecular layer is preserved and changed into a dense carpet of glia fibers, emerging from huge astrocytes, which are visible as dark spots. Similar gliosis is present in the underlying white matter (*A*). The external granular layer (*II*) shows in all stages a newly formed capillary network. The pyramidal layer (*III*) is free of nerve cells. The ground substance is fairly well preserved in the earliest stage (*A*) and severely destroyed in the final stage (*C*). The internal granular layer (*IV*), normally richest in blood vessels, is still visible in *A*, but is absent in *B* and *C*. In the two deepest layers (*V* and *VI*) sprouting capillaries form a lacelike network. The two interconnected capillary networks in layers *II* and *V* and *VI* are all that is finally left of the cortex. Laidlaw silver impregnation; × 50.

Cerebral Cortex: The meninges all over the brain were mildly and irregularly infiltrated with lymphocytes and macrophages containing hemosiderin. The pial vessels were filled with blood in all parts of the hemispheres, including the necrotic

area. No thrombi or emboli were observed anywhere. Within the diseased area the cortical myelin fibers were destroyed (fig. 2 *B*) and the architecture was completely lost. No neural elements were left. In place of the cortical layers an undifferentiated, amorphous, edematous, poorly stained expanse of ground substance was visible, filled with masses of compound granular bodies and phagocytes (fig. 3 *B*). In some places these cells too were degenerating (fig. 3 *C*). The marginal glia, consisting of giant fibrillary astrocytes and the molecular layers, was in most places preserved (fig. 3), but in certain regions a loose fibrous network was all that was left. Blood vessels represented the framework of the cortex. All blood vessels were in active proliferation, the smaller ones sprouting. In the regions of the second and fifth to sixth cortical layers two interconnected strands of richly growing capillaries formed an elegant lacelike pattern. The white matter underlying the diseased cortex showed scattered areas of beginning necrosis and liquefaction. No cavity formation and no sinking-in of the cortex was present. The border between the necrotic zone and the normal cortical structure was fairly sharp; a layer of mesodermal and glial elements formed a wall enclosing the diseased tissue.

Summary.—The histologic picture corresponded with that of incomplete softening of the cortex, with limitation of the destructive process to the parenchyma.

The left cerebral hemisphere presented various degrees of spongy disintegration, with mild damage to nerve cells and consequent glia reaction.

COMMENT

From a clinical standpoint this case presents many unusual features. The course of pathologic events may be summarized as follows:

At first, there was osteitis of the right lesser wing of the sphenoid bone. This inflammation spread across the sella turcica and gave rise to the changes in the optic nerves. After the operation on the sphenoid sinus there developed successively subarachnoid hemorrhage, basilar meningitis and involvement of the floor of the third ventricle, with consequent diabetes insipidus and changes in the cerebrum, which eventually led to generalized convulsions, high fever and death.

While meningitis is the commonest complication of infection of the paranasal sinuses, osteitis of the sphenoid bone is extremely rare. This case and another observed in the Graduate Hospital were the only 2 in the experience of Dr. G. M. Coates.[2]

That optic neuritis is not a rare complication of disease of the sphenoid and ethmoid sinuses is the opinion held by many clinical observers, although there are those who believe that retrobulbar neuritis is rarely, if ever, due to disease of the paranasal sinuses. In this case it was a striking feature in that the optic nerve atrophy developed during the period of our own observation in the hospital, in the course of a few days, undoubtedly as a result of the local inflammatory process around the optic chiasm and optic nerves.

Circumscribed and disseminated meningitides associated with sinal infection, as well as the "aseptic" and "protective" meningitis of otorhinogenic origin, are of common occurrence. In our case the infection in the sphenoid bone spread to the base of the brain, but the leptomeningeal

2. Coates, G. M.: Personal communication to the authors.

inflammation established a barrier preventing an inundation of the subarachnoid space by bacteria. The subarachnoid bleeding, on the other hand, was not accounted for by the necropsy observations. The terminal generalized convulsions could be explained by the severe widespread infection.

Hemiplegia as a complication of infection of the paranasal sinuses is caused usually by an intracerebral abscess, less commonly by an extradural or subdural abscess and most rarely of all by nonsuppurative encephalitis and thrombosis of the venous sinuses.[3] Occlusion of the middle cerebral or sylvian artery was not encountered in a compilation of 91 cases [4] of infection of the paranasal sinuses with neurologic complications.[3]

The diabetes insipidus was the most unusual clinical feature in this case. Diabetes insipidus occurs in association with epidemic encephalitis, basilar meningitis, fracture through the pituitary region, hypophysial tumors, metastatic tumors in the region of the floor of the third ventricle, craniopharyngioma and pinealoma, as well as idiopathic disease. Diabetes insipidus was not encountered in an analysis of 326 cases of neurologic complications accompanying infections both of the temporal bone and of the paranasal sinuses.[1] This syndrome must be ascribed in our case to the inflammatory lesion in the hypothalamic region.

The extent of the cortical lesion coincides with the distribution of the terminal branches of the sylvian artery, as described by Foix and Lévy.[5] No thrombus or embolus was found in the pial arteries over the damaged area; in fact, these vessels were full of blood. However, the right middle cerebral artery at its point of entrance into the sylvian artery was partially occluded by a marginal thrombus. Our sections did not permit us to determine whether the site of the thrombus was proximal or distal to the origin of the deep branches of this artery. The comparatively good preservation of the white matter speaks in favor of an occlusion distal to the point from which the large deep arteries arise.

Hence, the functional course of events leading to the incomplete softening of the cerebral cortex in the peripheral distribution of the sylvian artery seems to have been as follows: Basal meningitis, propagated from the sphenoid osteomyelitis, involved the right middle cerebral artery, producing periarteritis, arteritis and partial thrombosis. During operation a drop in blood pressure occurred because of hemorrhage from the sphenoid artery. Thus, the blood flow through the partially occluded middle cerebral artery was so much slowed that the blood supply in its terminal branches came to a standstill for several minutes. Anoxia and necrosis of the cortex was the consequence. With the return of the blood pressure to proper levels the blood resumed its former course beyond the area of incomplete thrombosis and was able to feed the mesodermal elements of the cortex, though too late to reverse the fate of its parenchyma.

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3. Beevor, C. E.: On the Distribution of the Different Arteries Supplying the Human Brain, Phil. Tr. Roy. Soc., London, s.B **200**:1, 1908.

4. Yaskin, J. C.: Localized Nonsuppurative Encephalitis Secondary to Infections of the Temporal Bone and Paranasal Sinuses, J. Nerv. & Ment. Dis. **92**:281, 1940.

5. Foix, C., and Lévy, M.: Les ramollissements sylviens, Rev. neurol. **2**:1, 1927.

A histologic picture almost identical with that seen in our case has been described by Hiller and Grinker [6] following passage of an embolus into the middle cerebral artery. No embolus, and no source for one, could be observed in our case.

The sharp limitation of the softening to the cortex might suggest that its arterial network was of the end artery type. This belief was, indeed, held by Beevor,[3] Heubner [7] and Duret.[8] However, Pfeiffer,[9] Cobb,[10] Craigie,[11] Freedom [12] and others were, with the help of modern methods of examination, able to show that there were abundant complex anastomoses between the cortical, the medullary and the basilar system of cerebral arteries. These anatomic studies gave, of course, no information as to the functional adequacy of the anastomotic connections. Sunderland [13] attempted to evaluate experimentally the "practical value" of the collateral cortical circulation. He determined in monkeys the number of anastomoses between pial and basilar arteries after circular isolation of cortical areas without interruption of the pial blood supply, on the one hand, and the effectiveness of the collateral circulation after obliteration of the pial arteries, on the other.

Sunderland came to the following conclusion: [13]

> When the blood supply to any cortical area is interrupted by obliterating the superficial pial vessels, no effective collateral circulation is established to the area either from deep ascending medullary vessels or from neighboring cortical areas.

In other words, the cerebral cortex receives its entire "effective supply" of blood from the pial system, and whatever anastomoses are present are functionally insufficient.

This experiment on the brain confirms previous experiences in general pathology. It is a well known fact that the arteries of many body organs, despite an extensive system of vascular anastomoses, behave like end arteries as soon as the blood pressure fails. Dietrich [14]

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6. Hiller, F., and Grinker, R. R.: Functional Circulatory Disturbances and Organic Obstruction of the Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **23**: 634 (April) 1930.

7. Heubner, J. B. O.: Die luetischen Erkrankungen der Gehirnarterien, Leipzig, F. C. W. Vogel, 1874.

8. Duret, H.: Quelques recherches récentes sur la circulation cérébrale, Encéphale **1**:7, 1910.

9. Pfeiffer, R. A.: Die Angioarchitektonik der Gehirnrinde, Berlin, Julius Springer, 1928; Grundlegende Untersuchungen für die Angioarchitektonik des menschlichen Gehirns, ibid., 1930.

10. Cobb, S.: The Cerebral Circulation: XIII. The Question of "End-Arteries" of the Brain and the Mechanism of Infarction, Arch. Neurol. & Psychiat. **25**:273 (Feb.) 1931.

11. Craigie, E. H.: Comparative Anatomy and Embryology of the Capillary Bed of the Central Nervous System, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:3, 1938.

12. Freedom, L.: Angioarchitektonik, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 1, p. 779.

13. Sunderland, F.: The Production of Cortical Lesions by Devascularization of Cortical Areas, J. Anat. **73**:120, 1938.

14. Dietrich, A., in Aschoff, L.: Pathologische Anatomie, ed. 6, Jena, Gustav Fischer, 1919, vol. 1, p. 493.

spoke of "functional end arteries." In addition, modern injection technic has demonstrated that many of these anastomoses are not patent except when under high vis a tergo. This is exactly what is missing in cases of low blood pressure. Even the opening of a collateral circulation would be of dubious value in the cerebral cortex, since its nerve cells do not survive an anoxic period of more than three to five minutes.

The result of combined clinical, pathologic and experimental experiences is that even temporarily insufficient blood flow in the terminal pial branches of one of the main cerebral arteries may lead to suffocation and eventually to death of the cortical nerve cells.

SUMMARY

1. A case of pansinusitis, purulent osteitis and necrosis of the right lesser wing of the sphenoid bone and the sella turcica, basilar meningitis with marked changes in the hypothalamic region and partial thrombotic occlusion of the right middle cerebral artery is reported.

2. The unusual clinical features include rapidly progressive optic nerve atrophy, subarachnoid bleeding, transient diabetes insipidus and hemiplegia. The pathogenesis of these manifestations is discussed.

3. The pathologic changes of the cerebral cortex in this case confirm the experience that the pial blood supply acts functionally as an end artery system, despite anatomic evidence to the contrary.

DISCUSSION

DR. A. M. ORNSTEEN, Philadelphia: Was the medial cerebral artery on the right side diseased prior to thrombosis?

DR. F. H. LEWEY, Philadelphia: Panarteritis apparently was the beginning of the arterial process and occlusion the secondary.

DR. A. M. ORNSTEEN, Philadelphia: Was occlusion general in all the cerebral arteries?

DR. F. H. LEWEY, Philadelphia: No, it was present in the right medial cerebral artery only.

News and Comment

FIFTEENTH GRADUATE FORTNIGHT, NEW YORK ACADEMY OF MEDICINE

The fifteenth Graduate Fortnight of the New York Academy of Medicine will be held in New York, Oct. 12 to 23, 1942. The subject will be "Disorders of the Nervous System."

The program includes morning panel discussions, afternoon clinics, evening lectures, scientific exhibits and demonstrations. The morning panel discussions will be held Tuesday and Friday of each week, at which questions relating to papers of the evening sessions will be discussed by a panel of invited authorities. A number of hospitals of the city will present clinical programs, in which distinguished clinicians from other staffs may participate.

Speakers at the evening lectures will include Drs. Timothy Leary, D. Denny-Brown, William Cone, E. Jefferson Browder, Edward A. Strecker, Harold G. Wolff, Donald Munro, Joseph E. J. King, Gilbert Horrax, Frank B. Walsh, Byron P. Stookey, Francis C. Grant, Stanley Cobb, Tracy J. Putnam, Charles D. Aring, Nolan D. C. Lewis, Walter Freeman, Lawrence S. Kubie, Henry A. Riley and William G. Lennox.

The registration fee is $5. Fellows of the Academy are registered without fee, by virtue of their membership.

A complete program will be mailed to every fellow without request and to other physicians on request. Address: 2 East One Hundred and Third Street, New York.

AMERICAN PSYCHIATRIC ASSOCIATION

At the ninety-eighth annual meeting of the American Psychiatric Association, held in Boston May 18 to 22, 1942, the following officers were elected: president, Arthur H. Ruggles, M.D., Providence, R. I.; president-elect, Edward A. Strecker, M.D., Philadelphia; secretary-treasurer, Winfred Overholser, M.D., Washington, D. C.; auditor, Charles W. Castner, M.D., Austin, Texas; councillors, James K. Hall, M.D., Richmond, Va.; Titus H. Harris, M.D., Galveston, Texas; Douglas A. Thom, M.D., Boston; Walter A. Treadway, M.D., Los Angeles.

SOUTHERN PSYCHIATRIC ASSOCIATION

Because of the difficulty of travel during the national emergency, it has been decided to hold the annual meeting of the Southern Psychiatric Association in Richmond, Va., on Nov. 6 and 7, 1942. These dates occur on the Friday and Saturday immediately preceding the annual convention of the Southern Medical Association, which meets in Richmond the week beginning November 8.

Dr. James K. Hall, of Westbrook Sanitarium, Richmond, is the chairman of the committee on local arrangements.

INTERNATIONAL LEAGUE AGAINST EPILEPSY

At the meeting of the American branch of the International League Against Epilepsy, held in Boston on May 18, 1942, the following officers were elected: president, Wilder G. Penfield, M.D., Montreal, Canada; vice president, Charles D. Aring, M.D., Cincinnati; secretary-treasurer, Frederic A. Gibbs, M.D., Boston.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

VERTICAL NYSTAGMUS FOLLOWING LESIONS OF THE CEREBELLAR VERMIS. E. A. SPIEGEL and N. P. SCALA, Arch. Ophth. **26**:661 (Oct.) 1941.

Spiegel and Scala made bilateral lesions of the vestibular nuclei in cats to study the effects of these lesions on the production of optokinetic nystagmus. It was noted that in some of the cats vertical or mixed vertical and rotary jerks appeared in addition to horizontal or mixed horizontal and rotary nystagmus, although histologic examination revealed that the lesions were limited to the caudal part of the vestibular nuclei. In analyzing this observation, it was necessary to bear in mind that one must elevate the posterior part of the vermis from the floor of the fourth ventricle or perforate parts of the cerebellum in order to place the lesions in the vestibular nuclei. Thus the question arose whether the appearance of vertical eye jerks was due to lesions of the cerebellum, especially of the posterior part of the vermis. Unfortunately, it is controversial whether cerebellar lesions are able to produce nystagmus, some authors denying and others affirming the occurrence of nystagmus caused by lesions restricted to the cerebellum. Those authors who were able to record the association of nystagmus with cerebellar lesions reported chiefly horizontal movements, while observations on vertical nystagmus were rare. Thomas noted vertical nystagmiform oscillations after extirpation of the vermis, without, however, excluding the importance of concomitant lesions, e. g., lesions of the corpora quadrigemina.

In view of the aforementioned experiment it seemed of interest to ascertain experimentally whether circumscribed lesions of the posterior parts of the vermis could produce vertical nystagmus.

The experiments were performed on 10 cats. The lobus posterior medianus cerebelli was exposed after excision of the posterior atlanto-occipital ligament and of the adjacent part of the occipital bone. By introducing small cotton pledgets between the medulla oblongata and the vermis, the latter was gradually elevated from the floor of the fourth ventricle, special care being taken to avoid a lesion of the fossa rhomboidea. The lobus posterior medianus was then cauterized while the floor of the ventricle was protected by a small sheet of rubber or cotton. In some experiments only the parts of the lobus posterior medianus were cauterized which could be exposed without separating the vermis from the ventricle. In other experiments the lobus posterior medianus was mechanically extirpated in order to avoid possible by-effects of the cauterization on the medulla oblongata. The operation was performed with the animal under ether anesthesia, so that the effects of the anesthetic would be only fleeting and those of the lesion could be watched as soon as possible after the operation. The eyeballs were observed not only with the head in the normal position but with the animal in side positions and in the supine position (vertex downward). The relation between the head and the trunk was kept constant during examination of the eyes by fixation of the animal on a board and of the head in a Czermak head holder, so that neck reflexes could not interfere. The extent of the lesions was studied microscopically, and in some animals serial sections were stained by Weil's method and with cresyl violet, respectively.

The authors state that the cats "showed that a cerebellar type of vertical nystagmus exists (besides that produced by lesions of the vestibular nuclei)" after lesions of the vermis. Further, "the intensity and to a certain degree the direction [of the nystagmus] are influenced by the position of the head." Their opinion as to its immediate cause was "release of the vestibulo-ocular reflex arcs from cerebellar inhibition."

SPAETH, Philadelphia.

TONIC NECK REFLEXES IN CLINICAL CASES OF HIGH AND LOW DECEREBRATE RIGIDITIES. J. M. NIELSEN and ARNOLD P. FRIEDMAN, Bull. Los Angeles Neurol. Soc. **6**:115 (Sept.) 1941.

Nielsen and Friedman describe 4 cases of spastic paralysis following sudden intracranial vascular lesions. In the first case convulsions began suddenly without unconsciousness, followed by extensor spasms of all extremities and clonic movements of the right side. Tonic neck reflexes were not present. Autopsy showed softening in the left side of the pons, with extension into the right cerebral peduncle. In the second case sudden loss of consciousness was associated with spastic flexion of the upper and extension of the lower extremities, with tonic and clonic movements of all the limbs. Turning the patient's chin to one side caused increased extension of the ipsilateral and relaxation of the contralateral extremities. Autopsy revealed a hemorrhage in the pons, extending into the mesencephalon. In the third case convulsive movements on the right side were followed by unconsciousness, deviation of the head and eyes to the right and spastic flexion of the right upper extremity and extension of all the others. Turning of the head to the right abolished and to the left increased the flexion of the right arm. Autopsy revealed recent vascular lesions in both internal capsules and an older one in the left side of the pons. In the fourth case stupor came on suddenly, followed by spasticity in extension and the Magnus-de Kleijn phenomenon in the upper left extremity, with skew deviation of the eyes. Autopsy revealed softening in the distribution of the right middle cerebral artery. Nielsen and Friedman conclude that the occurrence of decerebrate rigidity and the presence of tonic neck reflexes do not necessarily indicate a lesion in the brain stem. On the contrary, thrombosis of a major artery or subdural hematoma may cause indirect pressure on the brain stem and so produce these phenomena. They also believe that convulsions, apparently jacksonian in type, may be produced by lesions of the brain stem.

MACKAY, Chicago.

STUDIES ON ANEMIA IN DOGS DUE TO PYRIDOXINE DEFICIENCY. J. M. MCKIBBIN, A. E. SCHAEFER, D. V. FROST and C. A. ELVEHJEM, J. Biol. Chem. **142**:77, 1942.

The blood plasma iron is abnormally high in anemia due to pyridoxine deficiency in dogs. It drops to a low normal level during the remission with pyridoxine therapy. The total blood copper is at a low normal level during the anemia and increases to normal during pyridoxine therapy. After the immediate stimulation of blood formation afforded by pyridoxine therapy, there is a lag, which may be overcome by addition of liver extract to the ration. This stimulation is apparently not due to thiamine, riboflavin, nicotinic acid, pantothenic acid or choline.

PAGE, Indianapolis.

THE SIGN OF BABINSKI. KURT GOLDSTEIN, J. Nerv. & Ment. Dis. **93**:281 (March) 1941.

Recent work has shown that the appearance of the sign of Babinski is neither the expression of reversion to a phylogenetically more primitive reflex nor the result of the removal of the inhibition of cortical centers. On the contrary, there seems to be a correlation between the Babinski reaction and the importance of the forebrain in motor function. Goldstein expresses the opinion that the dorsal movement of the great toe is the essential element in the sign and that the fanning of the other toes is of a totally different character. The fact that this dorsal movement of the great toe has been elicited in conditions other than lesions of the pyramidal tract, such as peripheral neuritis, poliomyelitis and muscular atrophy, suggests to him that the sign of Babinski is the expression of a reversal of the normal ratio of sensitivity to stimulation of the flexor and the extensor muscles of the great toe. Further evidence in favor of this hypothesis comes from the fact that the Babinski sign can frequently be altered by changes in tone induced by alterations in posture.

Plantar flexion is the normal response because it is the reaction most useful to the organism in its normal activity. In its normal responses to unusual stimuli the organism utilizes a combination of voluntary and automatic reactions of flight and defense, and the defense reaction, representing an attempt of the entire healthy organism to deal effectively with the stimulus, may be regarded as the "higher" type of activity. Flight reactions come to the foreground and assume a special character when the organism is injured or defective. The Babinski sign represents a flight phenomenon depending on damage to the organism, especially to the pyramidal system. It also depends in large degree on the integrity of other regions of the nervous system and is most in evidence when the pyramidal tracts alone are damaged. It appears under these conditions only in the highest organisms, in which isolated movements play an important physiologic role. The normal response to plantar stimulation may be regarded as a rudiment of the physiologic grasping performance, the purpose of which is to recognize and deal with the object. The abnormal Babinski reaction represents a breakdown of performance from a higher to a lower stage of differentiation, i. e., from an ordered defense response to a more generalized and primitive flight reaction. Thus, the extensor response of the great toe is not a reversal of the "normal" plantar reflex but a pathologic reaction, while the normal response is a rudiment of a highly differentiated voluntary performance.

MACKAY, Chicago.

Neuropathology

LEAD ENCEPHALOPATHY SIMULATING DIFFUSE SCLEROSIS IN A CHINESE INFANT. W. J. C. VERHAART, Am. J. Dis. Child. **61**:1246 (June) 1941.

Verhaart reports a case of lead encephalopathy, with progressive development of spastic paralysis, involving first the legs, then the arms and finally the general body musculature. Examination revealed spastic tetraplegia with flexed arms and extended legs, high muscular tonus and pathologic plantar reflexes. There were many muscular twitchings. The pathologic picture was described as similar to that of diffuse sclerosis, but analysis of the brain and liver showed they contained large quantities of lead—270 and 315 mg., respectively, per kilogram of exsiccated matter. The author concludes that in the Netherland East Indies a diagnosis of diffuse sclerosis should not be made in the case of a child until saturnism has been excluded.

WAGGONER, Ann Arbor, Mich.

HISTOPATHOLOGICAL CHANGES IN EXPERIMENTAL METRAZOL CONVULSIONS IN MONKEYS. SILVANO ARIETI, Am. J. Psychiat. **98**:70 (July) 1941.

Arieti gave intravenous injections of a 10 per cent solution of metrazol to 5 monkeys for periods varying from thirteen to seventy-one days. Four of the animals died spontaneously during the course of the seizures, and the fifth was decapitated during a seizure. Histologic examination was carried out on the viscera and the nervous system. Arieti found alterations in the nerve cells in only 3 of the 5 monkeys, these changes varying considerably in intensity. He was unable to correlate in any way the duration of treatment, the dosage or the severity of the seizures with the pathologic changes. The lesions in the nerve cells were considerably milder than those occurring with insulin therapy: In 2 of the monkeys Pickworth stains showed marked changes in the vessels, particularly in the capillaries in an animal with spasm and in another with disintegration of the capillaries. These vascular modifications the author concluded were functional, and not responsible for the cellular changes. There were no areas of hemorrhage in the central nervous system. All the animals had nephritis, involving both the parenchyma and the interstitial tissues. In view of this, the author suggests the advisability of tests of renal function on patients before institution of metrazol therapy.

FORSTER, Boston.

THYMOMA IN MYASTHENIA GRAVIS. BARNES GILLESPIE, Arch. Path. **32**:659 (Oct.) 1941.

Weigert first described tumor of the thymus gland in cases of myasthenia gravis, and since then 58 cases have been recorded. In a typical case of myasthenia gravis reported by Gillespie microscopic examination of the thymus revealed a small tumor showing benign epithelial hyperplasia. He subscribes to the theory that the thymic tumor liberates a hormone which acts at the myoneural junction to destroy acetylcholine.

WINKELMAN, Philadelphia.

NEUROPATHOLOGIC CHANGES IN EXPERIMENTAL CARBON DISULFIDE POISONING IN CATS. ARMANDO FERRARO, GEORGE A. JERVIS and DAVID J. FLICKER, Arch. Path. **32**:723 (Nov.) 1941.

Emphasis has been laid repeatedly on the fact that symptoms and signs of involvement of the nervous system are outstanding in acute and chronic carbon disulfide poisoning. In acute poisoning, among the immediate effects are mental changes with acute delirium. In chronic poisoning, according to Ranelletti's work covering 100 patients, 80 per cent of the patients suffer from involvement of the nervous system; of these 52 per cent show mental changes, 10 per cent peripheral nerve lesions and 7 per cent extrapyramidal signs.

The authors exposed 5 cats to varying doses of carbon disulfide. They conclude as follows: The most important changes in carbon disulfide poisoning consist in (*a*) diffuse vascular involvement of the productive type, i. e., proliferation of capillaries and hypertrophy of the walls of blood vessels, often leading to endarteritis, and (b) diffuse neurocellular changes, ranging from chromatolysis to severe degeneration, diffusely scattered all over the brain and cerebellum.

Both cortical and subcortical structures are involved. The lesions are particularly evident in the corpora quadrigemina, the cerebellar nuclei and the vestibular nuclei. The region of the cerebellar nuclei is a particularly susceptible area, and in 4 of 5 cases the authors observed bilateral softening of this region. Next to the cerebellar nuclei, the vestibular area is most intensely involved. In an animal in which the exposure to the action of the gas was most prolonged, softening was also seen in the lenticular nucleus and in the substantia nigra.

WINKELMAN, Philadelphia.

Psychiatry and Psychopathology

ONE HUNDRED SCHIZOPHRENIC CASES OF LATE HOSPITALIZATION. LEO MALETZ and GRACE H. KENT, Am. J. Psychiat. **98**:173 (Sept.) 1941.

Maletz and Kent studied 100 patients with schizophrenia who were at least 45 years of age at the time of the first hospitalization. Eighty-five of the patients were women, 66 of the group were paranoid. Most of them had been self supporting. Forty-seven were unmarried. Forty of the patients were able to return to the community. Maletz and Kent point out that even though a person has reached middle life he is not necessarily immune from schizophrenia. Furthermore, if the acute attack is survived, the prognosis in such cases is not bad.

FORSTER, Boston.

EEG STUDIES OF NINE CASES WITH MAJOR PSYCHOSES RECEIVING METRAZOL. KNOX H. FINLEY and JOSEPH M. LESKO, Am. J. Psychiat. **98**:185 (Sept.) 1941.

The electroencephalographic patterns of the human subject after a single intravenous injection of metrazol was found by Finley and Lesko to have four phases. The first phase lasts five to fifteen seconds and is characterized by slow waves. The second phase begins with the sudden appearance of high voltage spike waves, corresponding to the chronic stage of the convulsion, and is gradually replaced by a decreasing frequency of the spike potentials, corresponding to the chronic

phase. The average duration of this phase is fifty seconds. The third phase develops abruptly with a depression of the cortical potentials of the second phase and has an average duration of thirty seconds. In the fourth phase slow random waves appear, tending gradually to be supplanted by the normal electroencephalographic pattern. The duration of phase 4 varies from thirty minutes to four hours.

The electroencephalographic tracings of 9 patients who had received metrazol three or more days prior to the studies were examined. These records could be divided into three groups as follows: Group 1: The electroencephalogram showed improvement or remained unaltered. This included the records of 4 patients who had received 6 or less injections of metrazol. Group 2: The electroencephalographic tracings showed changes of a temporary character. This included the records of 3 patients who had received 9 to 14 injections. Group 3: The electroencephalographic tracings showed abnormal changes of a permanent character. This included the records of 2 patients who had received 18 to 20 injections, respectively.

FORSTER, Boston.

SHOCK THERAPY IN PSYCHOSIS COMPLICATING PREGNANCY. H. H. GOLDSTEIN, J. WEINBERG and M. I. SANKSTONE, Am. J. Psychiat. **98**:201 (Sept.) 1941.

Goldstein, Weinberg and Sankstone report the case of a woman, approximately 3½ months pregnant, who was admitted to a hospital with a psychosis characterized by delusional ideas, depression and mutism. Thirteen convulsive seizures were induced by metrazol. After this the patient was given insulin therapy for thirteen days without the production of coma. The patient was delivered of a normal, full term child; nine months after the delivery the child was apparently well, while the mother was still institutionalized.

FORSTER, Boston.

PSYCHIATRIC RESULTANTS OF ALCOHOLISM: ALCOHOLISM AND MENTAL DISEASE. NOLAN D. C. LEWIS, Quart. J. Stud. on Alcohol **11**:293 (Sept.) 1941.

Lewis discusses the psychotic reactions to alcohol from the viewpoint of clinical experience. He notes that the terms which have been in use for years are merely descriptive of certain constellations of events and reactions, while additional research will probably allow for a more comprehensive arrangement on the basis of specific etiologic factors, pathologic changes and individual differences in reactions. He considers each of the clinical concepts in turn, beginning with that of "pathological intoxication." He notes that the Korsakoff reaction rarely, if ever, follows acute alcoholic hallucinosis, as it does delirium tremens, but adds that acute alcoholic hallucinosis may go on to schizophrenia. Many of these conditions are difficult to differentiate from schizophrenia with confusion, and Lewis wonders whether many of them are attacks of schizophrenia colored by alcoholic bouts in order to relieve the conflict. He states that when alcohol is the principal factor there is more insight after recovery than is found in schizophrenia. It is possible that the condition is latent schizophrenia, the total picture being due to the following formula: latent schizophrenia plus chronic alcoholism plus metabolic disorder plus acute alcoholic excesses equals acute alcoholic hallucinosis.

The author also calls attention to the fact that the excessive use of alcohol may precipitate simple depressions, manic-depressive outbreaks, catatonic pictures and epileptic reactions. The old belief that alcohol was the direct cause of specific psychoses has met with recent growing skepticism. In cases of delirium tremens and of some other conditions the alcohol has usually been excreted and metabolized long before the mental reaction returns to normal. The "hang-over" with its mental symptoms indicates some factor in addition to the alcohol, and the drunken state with its clinical expressions does not always correspond to the alcohol content of the blood. The individual factor is foremost. The alcoholic psychosis represents a combination of inherited factors, the physical condition, including the metabolic state, personality features, the life experience and the toxic effects of alcohol.

BRACELAND, Chicago.

A Note on the Validity of Certain Rorschach Symbols. C. J. C. Earl, Rorschach Research Exchange **5**:61 (April) 1941.

Earl attempted to test the validity of his interpretations of certain symbols occurring in Rorschach responses. He attaches symbolic significance to the responses when they indicate the presence of a fantasy process (M, FM, m) or of a greater or lesser degree of inner disturbance (K, KF, FK) but little, if any, symbolic importance to pure F responses unless there is some important reason for doing so. In this study he also tested especially the symbolic significance of water responses in records taken from unstable boys known to be markedly infantile in the emotional sphere. The subjects were a small group of unstable boys, aged 13 to 15 years, all of at least borderline intelligence. A factor common to all was severe conflict over masturbation.

A few hours to a few weeks after the Rorschach test the subjects were hypnotized and directed to give associations to thoughts presented to them, among which were significant responses from their Rorschach tests.

In a high percentage of cases the hypnotic association to the significant responses verified the validity of the interpretation either directly or by the presence of marked inhibition or anxiety. The contents of some of the symbols were castration, masturbation, mutual masturbation, sexual intercourse, oral erotism and anxiety.

Marcovitz, Philadelphia.

An Evaluation of Personality Analysis in the General Practice of Medicine. George G. Holzman and Evelyn E. Holzman, Rorschach Research Exchange **5**:67 (April) 1941.

In addition to the psychiatrist and the neurologist, the general practitioner is called on to differentiate functional disorders and to treat patients with less severe forms of such disturbances who respond readily to mild medication or to advice as well as those whose signs and symptoms are numerous and who are not quick to respond to superficial treatment.

In order to determine the best possible approach to such patients, a detailed study of the origin of the disorder is essential, in order to place each patient in the proper group, either that of mild disorders which the practitioner feels he himself can treat or in the group of more severe disorders which require specialized psychiatric care. Because this investigation and segregation usually require more time and training than the general practitioner possesses, a definite diagnostic procedure is necessary. Such a procedure is afforded by the Rorschach method, which enables the physician to understand the patient's psychologic makeup and reveals his conflicts, his emotional capabilities and a relative degree of his intelligence, as well as his orientation to his environment. All this becomes apparent in a short time, perhaps from ten to sixty minutes or longer, depending on the number and complexity of the responses.

Marcovitz, Philadelphia.

An Experimental Study of the Reliability of the Rorschach Psychodiagnostic Technique. Irving Arthur Fosberg, Rorschach Research Exchange **5**:72 (April) 1941.

Although the Rorschach test is accepted automatically by all Rorschach enthusiasts in determining and measuring personality, its reliability has not as yet been established by any other study. Fosberg attempts to supply such a control by (*a*) a review of published data that might throw light on the question of reliability, (*b*) the calculation of coefficients of reliability for 26 cases published in the literature in which original Rorschach protocols were presented for two or more tests (the control group), (*c*) an experiment with 37 subjects using the Bernreuter inventory and the same type of instructions as were later given to the subjects in the Rorschach experimental groups, and (*d*) an experiment on 66 subjects using the Rorschach test.

In the Rorschach "control" group consisting of 26 persons for whom the protocols for two or more tests had been published, reliability coefficients for the three Rorschach sections, *Erfassungsmodi*, content and determinants, as well as for the total test, were high and compared favorably with the correlations reported for other personality tests.

Thirty-seven subjects were given the Bernreuter inventory, first under standard conditions, then under instructions to make a "good" impression, and later a "bad" impression, of their personalities and, finally, again under standard conditions. It was found that the subject could easily manipulate the test.

However, when the test was then given to three groups (1) male experiment group (25 subjects), (2) female experimental group (25 subjects) and (3) special experimental group (6 male and 10 female subjects), all of whom had at least attained a second year academic standing and at least one year of psychology in college, the results indicated that the Rorschach test could not be manipulated by the subject.

The test-retest reliability of the Rorschach psychodiagnostic technic is high. The Rorschach test cannot be prompted by the experimenter. Finally, all the correlations obtained in this experiment were found to be reliable.

MARCOVITZ, Philadelphia.

PSYCHIATRIC FACTORS IN THE MEDICAL EXAMINATION. JOSEPH H. PRATT, War Med. **1**:358 (May) 1941.

Pratt draws attention to the importance of collecting a satisfactory social history as a means of determining the fitness of a draftee. This social history, which could be secured by a clerk attached to each examining board, should contain information about the following factors: 1. Intelligence, determined by ascertaining the grade the draftee reached in school. 2. Past health, obtained from the family physician or from the hospital or dispensary where the draftee has been treated for the last five years. A history of frequent visits for medical advice, reassurance or minor complaints by a man whose physical examination shows he is normal warrants his rejection. 3. Character. A history of arrests for minor offenses or of reform school residence should warrant the rigid exclusion of the draftee. 4. Occupational record. A history of frequent changes of occupation is often found in cases of psychoneurotic or psychotic persons.

PEARSON, Philadelphia.

EFFORT SYNDROME IN SOLDIERS. JOHN PARKINSON, Brit. M. J. **1**:545 (April 12) 1941.

Effort syndrome is tentatively defined as a functional circulatory disease, most evident on exertion, which is unmasked or produced by war service. The writer hopes that the experience of the present war will produce a better name, a more satisfying definition and a clearer understanding of the condition. The causes of the syndrome are often multiple and may be constitutional, psychoneurotic, infectious or myocardial. Symptoms likewise are multiple and include exhaustion, pain in the left mammary region, palpitation, dyspnea, dizziness and faintness. The patient may be nervous, anxious, fatigued or seemingly well. Among the common signs are tachycardia and sweating. The heart and the blood pressure are normal. The condition must be differentiated from organic heart disease, neurosis, pulmonary tuberculosis, hyperthyroidism, hypertension, chronic bronchitis, emphysema, asthma, pleurisy, anemia, renal disease, aural vertigo and epilepsy. The prognosis depends on the duration of the disease and the desire of the patient to overcome it. About 50 per cent of the victims during the first World War recovered. Many cases of this condition can be prevented by proper selection of recruits and rejection of potential subjects. Psychologic treatment is recommended.

ECHOLS, New Orleans.

THE MENTAL DEFECTIVE IN THE ARMY. F. J. S. ESHER, Brit. M. J. **2**:187 (Aug. 9) 1941.

Esher calls attention to the fact that mental defectives are a hindrance to the efficiency of a modern army because they are slow to learn, prone to breakdown, frequently report sick and are a potential danger. These men can easily be detected by intelligence tests. Also, their work history and capacity for learning are indications of their mental ability. Esher recommends that all men with a mental age of less than 10 years should be rejected from the army. However, he points out that they can and should perform useful tasks in civil life, such as repetitive work and "blind alley" jobs.

ECHOLS, New Orleans.

Diseases of the Brain

DISTURBANCES OF BEHAVIOR IN PATIENTS WITH DISSEMINATED SCLEROSIS. ORTHELLO R. LANGWORTHY, LAWRENCE C. KOLB and SERGE ANDROP, Am. J. Psychiat. **98**:243 (Sept.) 1941.

Langworthy, Kolb and Androp found in a series of 199 patients with multiple sclerosis 56 in whom notable disturbances of behavior had developed. Sixteen of this group had to be admitted to psychiatric institutions. The authors divide the patients into groups as follows: (1) patients with a diagnosis of hysteria; (2) patients with difficult social adjustments; (3) patients with marked organic disturbances and mild behavior difficulties, and (4) patients with major behavior disorders. The authors emphasize the frequency with which the initial symptoms of multiple sclerosis are mistaken for hysterical or neurotic symptoms and stress the frequency of emotional instability as compared with mental deterioration. They point out that heredity and the previous background of the patient must be considered, as well as his personal reaction to the disability.

FORSTER, Boston.

MORTALITY FROM ALCOHOLISM IN THE UNITED STATES. CALVIN F. SCHMID, Quart. J. Stud. on Alcohol **1**:432 (Dec.) 1940.

Schmid points out some of the difficulties attendant on a statistical survey of the mortality from alcoholism. Because of the stigma attached, physicians are prone even in definitive cases of alcoholism to substitute a less obnoxious cause on the death certificate. It is impossible to measure the total mortality from alcoholism; so the author uses his data to evaluate the relative incidence of mortality from alcoholism for various classes of the population or for geographic areas. Throughout the United States in 1938, alcoholism was diagnosed as the primary cause of death in 2,569 cases. In addition, there were 959 deaths from alcoholic cirrhosis of the liver. The first figure given comprises 0.2 per cent of the total death rate, or 2.0 per hundred thousand of the population. All things considered, the trend in mortality from alcoholism is downward. In 1900 the death rate was over 6.0 per hundred thousand. The highest death rate from alcoholism was reached in 1907; the lowest rate coincided with the early years of the prohibition era. The author's figures show that over a five year period 87.9 per cent of the fatalities were in males and 12.1 per cent in females. The peak is reached at the age of 50 to 54 years for men and 35 to 39 years for women. The death rates for cirrhosis of the liver are almost twice as high for men as for women.

Geographically, Nevada, with a mean rate of 12.5 per hundred thousand, has the highest incidence of death from alcoholism. Delaware is second, with a rate of 5.6 per hundred thousand. The high rate in Nevada is probably influenced in part by the large number of nonresident deaths. Fifteen contiguous states in the Middle West and South have very low rates. Mississippi and Louisiana, each with a rate of 1.1 per hundred thousand of population, recorded the lowest mortality from alcoholism during the five year period 1934 to 1938.

BRACELAND, Chicago.

ALCOHOL AND EPILEPSY. WILLIAM G. LENNOX, Quart. J. Stud. on Alcohol **2**:1 (June) 1941.

Lennox studied the extent of the use of alcohol by persons subject to epilepsy and the effect of alcohol on their seizures. As yet there have not been satisfactory data from extramural patients. The report of Craig Colony of New York for the years 1936-1940 inclusive listed 1,570 first admissions. Of this number of patients, alcohol was listed as a cause of epilepsy in 4.3 per cent, and was regarded as the primary cause in 2.1 per cent. Lennox and his collaborators examined the records of approximately 2,000 patients, all of whom were subject to seizures. Of the 1,254 patients who answered the questions satisfactorily, 24 per cent said that the amount of alcohol they used was small and 8 per cent said it was large. The 8 per cent of large users in the extramural group approximated the 6 per cent of intemperate users entering Craig Colony. Lennox states that although his control group was not especially satisfactory, it indicated that epileptic patients do not use more alcohol than those who are unaffected.

Lennox also analyzed the group according to age and sex to determine the influence of these factors in the effect of alcohol on seizures. The number in whom alcohol was observed to be a factor in producing seizures was 6 per cent of all patients and 21 per cent of those who used alcohol. The proportion was greater among males than among females and among patients with symptomatic than among those with essential epilepsy. The proportion who experienced seizures after the use of alcohol was less among older patients and was much greater among patients who used alcohol frequently than among those who used it infrequently. In the group of frequent users 57 per cent reported that seizures sometimes or frequently followed indulgence. From the author's own observation of individual patients he knows that petit mal episodes are made worse by even small amounts of liquor.

Lennox concludes that the physiologic or chemical mechanism by which alcohol produces seizures in the "sobering-up" period in predisposed persons is not clear. He states that the need for an electroencephalographic survey of alcoholic patients and their relatives is urgent.

BRACELAND, Chicago.

EPILOIA. L. M. QUILL and E. C. MARTING, Surgery **9**:581 (April) 1941.

Quill and Marting describe the syndrome of epiloia observed in 7 persons of three generations. Although the mother of the first and seventh patients (the grandmother of the other 5 patients) was not examined clinically, the history of epileptic seizures, adenoma sebaceum and tumors of the nail bed makes the diagnosis of epiloia a valid presumption. If this is granted, the study reveals direct passage of the disease through three generations. The study discloses that if the patient with epiloia lives through puberty and is capable of mating transmission of the disease is possible. The reason for so few examples of transmission lies in the fact that the average affected patient is so mentally and physically incapacitated at puberty that marriage and mating do not occur. Study of the family tree discloses that 1 daughter (case 1) of the patient with the original case of epiloia transmitted the disease in all its intensity to all 4 of her children who lived to puberty, whereas the other daughter (case 7) with signs of the disease apparently did not pass it on to her 2 older children. There is no evidence of the disease in the other 2 children of the patient with the original case of epiloia. Neither was the condition found in their children. This suggests that the disease is not recessive, but rather is incompletely dominant. The tumors of the nail bed, usually an uncommon accompaniment, are of particular interest because of their presence in all 7 cases. The presumption here is that epiloia is transmitted, even in its minute details. The direct transmission of the disease from parent to offspring through three generations proves that the syndrome is hereditary, i. e., genotypical, as suggested by Fabing.

J. A. M. A.

TRAUMATIC EPILEPSY AFTER GUNSHOT WOUNDS OF THE HEAD. P. B. ASCROFT, Brit. M. J. **1**:739 (May 17) 1941.

Ascroft analyzes in detail 317 cases of gunshot wound of the head occurring during the first World War with regard to the occurrence of epilepsy. The patients were followed from seven to twenty years after injury. Of the entire series, epilepsy developed in 34 per cent. Fourteen of the patients died, but only 2 as the result of a complication of the brain injury. Analysis of the cases suggested the following conclusions: In cases of penetrating wounds the presence of a small piece of metal in the brain does not increase the risk of epilepsy; head wounds due to projectiles are more likely to be accompanied by local damage to the brain, and therefore epilepsy, than head wounds encountered in civil practice; fits are commoner when the wound is septic; wounds in and about the rolandic area are most often followed by fits and polar wounds least often; the presence or absence of concussion after a gunshot wound does not influence the subsequent liability to epilepsy; convulsions begin more often in the first two weeks after injury; attacks eventually subside most often when the fits begin in the first two weeks after injury, less frequently when fits begin within the first two years and never when they occur more than two years after injury.

ECHOLS, New Orleans.

ETIOLOGY OF TICK (SPRING-SUMMER) ENCEPHALITIS. W. D. SOLOWJOW, Acta med. URSS (no. 4) **3**:484, 1940.

Solowjow reports that in recent years a peculiar form of encephalitis has been observed in the forest regions of Siberia. It begins suddenly with high fever, severe headache, vertigo and vomiting. Together with meningeal symptoms, localized signs of involvement of the central nervous system develop in the form of paralysis of the upper and lower extremities and of the musculature of the neck and back. The fever persists for four to ten days. Some patients retain permanent atrophic paralysis, particularly of the proximal portions of the upper extremities and of the musculature of the neck and shoulder regions. The mortality is 30 per cent. The pathoanatomic changes in the central nervous system recall descriptions of the Japanese (summer) encephalitis and of the American (St. Louis) encephalitis. The epidemiologic picture of tick encephalitis is characterized by the strict seasonal character. It begins about the end of April, reaches its severest stage by the end of May and the first part of June and then declines, only a few sporadic cases occurring after July. The appearance of tick encephalitis seems to be connected with work in the taiga (swampy forests of Siberia), particularly with the sartage of these regions. The climatic conditions at the time of occurrence are characterized by moderate temperature, high humidity and considerable precipitation. The chief epidemiologic characteristics can be explained by the existence of vectors—that is, ticks of the family Ixodidae. The seasonal occurrence of tick encephalitis follows the period of maximal activity of these ticks. The vector role of the ticks was demonstrated by the detection of spontaneously infected Ixodes persulcatus in the regions where the disease was endemic, by long survival of the virus in artificially infected ticks, by virus transmission by bite and by virus transmission by the transovarian route and in the course of metamorphosis. At the same time that the ticks were studied the possibility of a virus reservoir among the forest mammals was investigated, and it was found that some rodents and insectivores harbor the virus. A considerable percentage of human subjects living in the region where the disease was endemic had a neutralizing antibody content against the encephalitis virus, and the serum of cattle, horses and other animals disclosed the same protection. Tick encephalitis is caused by a neurotropic, filtrable virus, which is pathogenic for white mice, monkeys, some rodents and birds. The most reliable method of culturing the virus is transmission to the mouse of a brain emulsion from human beings who have died of the encephalitis. The virus resembles the causal agents of other seasonal forms of encephalitis (Japanese and

St. Louis) and differs from them in certain serologic characteristics. The author thinks that the reported studies permit the assumption that the causal agent of tick encephalitis is a specific ultravirus closely related to that of Japanese summer encephalitis.

J. A. M. A.

Vegetative and Endocrine Systems

THE EFFECT OF TESTOSTERONE PROPIONATE ON THE RAT TESTIS. H. S. RUBINSTEIN and A. A. KURLAND, Endocrinology **28**:495 (March) 1941.

Testosterone propionate, in doses varying from 0.005 to 2.5 mg., was given to 22 day old rats daily for ten days. The smallest doses led to a significant increase in the weight of the testes. With larger doses testicular weight was decreased, but with doses in excess of 0.05 mg. the degree of depression was inversely proportional to the size of the dose.

Doses (0.05 mg.) that were depressing when used for short periods failed to depress the testis when continued over longer intervals, presumably owing to dilution of androgen concentration as a result of the added body growth. It is suggested that small doses stimulate proliferation of the germinal epithelium. Larger doses inhibit testicular growth by depressing the function of the pituitary gland. Further increase in the dose results in such an increase in the size of the reacting secondary sex organs that much of the injected androgen is utilized merely for their maintenance, thus sparing the testis. PALMER, Philadelphia.

SPONTANEOUS HYPOGLYCEMIA AND THE HYPOPHYSIS. E. MEYTHALER, Deutsche med. Wchnschr. **67**:433 (April 18) 1941.

Meythaler believes that the role of the liver in the intermediary carbohydrate metabolism, with its dependence on neurohormonal regulation, by the diencephalohypophysial system and the incretory glands is responsible for the disturbances in the regulation and equilibrium which lead to spontaneous hypoglycemia. He presents the history of a woman aged 46 who for six years had been subject to attacks characterized by weakness, loss of memory, fainting and somnolence. The attacks occurred as a rule before the noon meal. Severe hypoglycemia was discovered to be the cause of these attacks. The author attempts to prove that the severe spontaneous hypoglycemia in this case was due to relative hyperinsulinism, which in turn developed because of a disturbance in hormonal correlation between the diencephalohypophysial system and the other secretory glands. The eliciting factor in the hypoglycemia was the hypofunctioning of the anterior lobe of the hypophysis, which in turn was the sequel of many years of excessive demands on this organ following early total extirpation of the uterus and its adnexa (at the age of 23). By the time the woman reached the period of the physiologic climacteric, the anterior lobe of the hypophysis was so exhausted that the pancreas became dominant.

J. A. M. A.

ROLE OF HYPOPHYSIS IN CARBOHYDRATE METABOLISM. T. SAKAI, Tokyo Igakkwai Zassi **55**:189 (March) 1941.

Sakai started his investigations on the function of the hypophysis in carbohydrate metabolism by first observing sugar assimilation in 14 cases of acromegaly, in 64.3 per cent of which he found glycosuria. In over half of these cases the glycosuria was found to be renal, with a spontaneous and markedly fluctuating elevation of the excretory threshold. In all cases in which glycosuria was present the duration of the disease had been more than ten years. In only 3 cases was there fasting hyperglycemia, with definite lowering of sugar tolerance. Sakai believes that hyperglycemia associated with acromegaly is extrainsular in origin. The second phase of his studies deals with the observations on sugar metabolism in patients with disturbance in the anterior lobe of the pituitary. Of 9 cases of

dwarfism, 4 cases of cachexia, 3 cases of polyglandular deficiency, 2 cases of eunuchoidism and 3 cases of dystrophia adiposogenitalis, disturbances in sugar metabolism, such as delayed restoration of a normal blood sugar level after alimentary hyperglycemia, slow development of epinephrine hyperglycemia, glycosuria and reelevation of both sugar tolerance and excretory threshold, were exhibited in the majority. In a further study of sugar metabolism in 6 cases of diabetes insipidus the author found practically no evidence of disturbed sugar metabolism. In 10 cases of hypophysial dysfunction without association of endocrine disturbance, Sakai found 2 cases in which symptoms of dysfunction of the anterior lobe during pregnancy with renal glycosuria were presented; this he explained on the basis of the pregnancy cell nodule hypothesis of Erdheim. In the experimental animal (rabbit) the author produced immediate elevation of the threshold for sugar excretion by the intravenous or subcutaneous injection of gonadotropin. One or one and a half months after the subcutaneous injection the threshold was gradually lowered, and repeated administrations at this stage no longer produced elevation. Identical results were obtained with a similar injection of adrenal cortex extract. These observations prove that elevation of the renal threshold produces marked alimentary hyperglycemia and that the metabolic function is at its best when the renal threshold is low.

J. A. M. A.

Treatment, Neurosurgery

EFFECT OF BENZEDRINE SULPHATE ALTERNATED WITH SODIUM AMYTAL IN SCHIZOPHRENIA. LEON REZNIKOFF, Am. J. Psychiat. **98**:196 (Sept.) 1941.

Reznikoff treated a group of 15 schizophrenic patients with sodium amytal and with parenteral injections of benzedrine sulfate on alternate days. No improvement was noted in any of the patients treated in this manner for a month or longer.

FORSTER, Boston.

AMPHETAMINE (BENZEDRINE) SULFATE AS A CORRECTIVE FOR THE DEPRESSION OF SEDATIVE MEDICATION IN EPILEPSY. LEON J. ROBINSON, Am. J. Psychiat. **98**:215 (Sept.) 1941.

Robinson administered amphetamine (benzedrine) sulfate in doses of 5 to 30 mg. to 58 patients with epilepsy who had manifested toxic symptoms due to anticonvulsant medication, chiefly with phenobarbital. These symptoms consisted of drowsiness, ataxia, irritability, aggressiveness, anorexia, vertigo, nystagmus and tremor. Thirty-nine of the 58 patients were relieved of their toxic symptoms by amphetamine sulfate, and in 21 of these 39 patients it was necessary to administer the drug only temporarily. The frequency of seizures was not altered by the use of amphetamine. Robinson concluded that amphetamine sulfate is of especial value in allowing an increase in the anticonvulsant medication beyond that otherwise tolerated by the patient.

FORSTER, Boston.

EFFECT OF VITAMIN B COMPLEX ON RESIDUAL NEURAL DISTURBANCES OF TREATED PERNICIOUS ANEMIA. J. C. ZILLHARDT, I. HOWARD and W. P. MURPHY, Ann. Int. Med. **15**:44 (July) 1941.

Zillhardt and his associates, on the basis of 19 cases about equally divided as to sex, report the temporary beneficial effects of vitamin B_1 on residual neural signs and symptoms of pernicious anemia which seemed stationary in spite of persistent and intensive anti-pernicious-anemia therapy. The principal improvements noted on physical examination were in temperature sense, pain sense and two point discrimination and occurred only during the first two months of an experimental period of four months. Three thousand international units of thiamine hydrochloride administered intravenously was found to be more effective than 900 international units given orally twice a day. The many variables involved in attempting to quantitate neurologic symptoms and signs were carefully considered.

Since the intramuscular use of thiamine seemed to benefit most of the patients, the authors believe that with such treatment the efficiency of undamaged neural tissue might become increased or existing reversible peripheral neuritic changes become improved or, as a result of the possible improvement of the patient's general health, neural function might become enhanced. J. A. M. A.

INTRACRANIAL USE OF SULFONAMIDES: EXPERIMENTAL STUDY OF HISTOLOGY AND RATE OF ABSORPTION. E. F. HURTEAU, Canad. M. A. J. **44**:352 (April) 1941.

Hurteau inserted powdered sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) or sulfathiazole (2-[paraaminobenzenesulfonamido]-pyridine) into one of two cerebral wounds made in 25 cats. The other wound was used as a control. The operations were carried out under aseptic technic. The results obtained rule out any contraindications to the use of these drugs in this manner. There were accumulations of polymorphonuclear leukocytes about the meninges in several cats inconsistent with observations on others. The distribution of these accumulations and the fact that they were present in both wounds and remained in the treated wound after the drug was completely absorbed suggested that they were due to the presence of foreign bodies (silver clips and sutures). This was proved conclusively in 2 cats in which a silver clip was placed in the wound without the drug but not in the wound containing the drug and the leukocyte reaction was seen only about the silver clip. The drug was seen macroscopically or microscopically as late as twenty days. The drug even while present caused but a minimal focal foreign body reaction. There was no constant evidence of neuron destruction or glial reaction resulting from its application to incised cerebral wounds. The ultimate healing of wounds in no way suggested that the drugs increase scarring or are carcinogenic. Sulfapyridine was the slowest to be absorbed but could not be detected after thirty-four days; sulfathiazole could not be detected after seventeen days or sulfanilamide after eleven days. J. A. M. A.

VITAMIN B_6 FOR SYDENHAM'S CHOREA. J. SCHWARTZMAN, D. DRAGUTSKY and G. ROOK, J. Pediat. **19**:201 (Aug.) 1941.

Schwartzman and his associates used vitamin B_6 (pyridoxine) for the treatment of 3 patients with Sydenham's chorea. The amount of pyridoxine hydrochloride necessary for a satisfactory response for each of the 3 patients was 180, 425 and 840 mg., respectively. Improvement was not discernible until the patient had been under treatment for several days, and it was gradual at first; the intensity of involuntary movements was diminished, and a feeling of general comfort and restfulness followed. Once improvement began, the amelioration of symptoms was progressively increased. No reactions were encountered. The simplicity of the treatment lends itself to home care. The dramatic response of these patients to vitamin B_6 suggests that one of the etiologic factors in chorea may be a vitamin deficiency. Preliminary reports of cures should not be accepted until full verification is had from additional reports. J. A. M. A.

A STUDY OF THE USE OF CURARE IN METRAZOL CONVULSANT THERAPY WITH SOME ELECTROENCEPHALOGRAPHIC OBSERVATIONS. M. M. HARRIS, B. L. PACELLA and W. A. HORWITZ, Psychiatric Quart. **15**:537 (July) 1941.

The authors studied 11 patients curarized preceding each administration of metrazol to the point of paresis of the muscles of the neck. Roentgenograms of the spine were made before and after the course of curare and metrazol therapy. Except for the diminution of muscular contractions, the responses resembled those to metrazol alone. The authors found no marked alleviation of apprehension, such as was reported by Bennett. The results were considered comparable to those found with unmodified metrazol treatment. With the preparation used few untoward reactions occurred. The blood pressure was unchanged. Laryngeal

stridor and respiratory depression responded to artificial respiration. One patient had a delayed respiratory crisis and showed alarming symptoms, which, too, responded to artificial respiration. No fractures occurred. Electroencephalograms did not differ from those of patients receiving metrazol alone.

SIMON, Middletown, Conn.

A CONVULSION DURING NON-CONVULSIVE FARADIC SHOCK THERAPY. GERALD CAPLAN, Brit. M. J. **1**:479 (March 29) 1941.

Caplan briefly describes the technic of nonconvulsive faradic shock treatment of mental diseases. He states that not only have the results been as good as those of ordinary metrazol or electrical convulsive therapy but the dangers attending convulsions have been obviated. He reports a case of acute mania in which the patient was being successfully treated by this method. Return to normal was noted within six days, but the patient became so sensitized to the faradic current that eventually a major convulsion was produced by a potential only a fiftieth the strength of that used in standard electric convulsive therapy.

ECHOLS, New Orleans.

EXPERIENCES IN TREATMENT OF PERIPHERAL NERVE INJURIES WITH AMNIOPLASTIN. LAMBERT ROGERS, Brit. M. J. **1**:587 (April 19) 1941.

Experiments by Penfield and others have shown that amnioplastin is the best substance for preventing a damaged structure from becoming adherent to adjacent tissues. This material, which is absorbed in about three weeks, is prepared from human amniotic membrane and preserved in 70 per cent alcohol. The technic of its use in nerve surgery consists of isolating and freeing the nerve trunk from the scar tissue above and below the level of the lesion. After a dry field is obtained, the site of the lesion is wrapped with a sheet of amnioplastin large enough to extend beyond the limits of the lesion. Rogers reports gratifying and encouraging results with the use of this substance in 12 cases of peripheral nerve injury and has also used it to protect the brain in 8 cases.

ECHOLS, New Orleans.

TREATMENT OF APOPLEXY. R. SINGER, Wien. klin. Wchnschr. **54**:65 (Jan. 24) 1941.

Singer points out that in the presence of arteriosclerosis of the cerebral vessels necropsy frequently discloses cerebral edema. It seemed reasonable to expect that removal of this edema would be followed by improvement. Since myocardial damage is likewise frequent in cases of apoplexy, it seemed advisable to improve the action of the dehydrating agent by simultaneous administration of digitalis. The author gives the apoplectic patient an intravenous injection of 1 cc. of salyrgan. The injection is repeated up to five times at intervals of from five to seven days, and the dose is increased to 2 cc. Patients who seemed to be in a hopeless condition, such as those with a ventricular hemorrhage, those whose condition became noticeably worse in the course of three days of observation and those in whom the apoplexy had existed for more than three weeks, were not subjected to this therapy. It was employed for 28 patients, whose ages ranged from 34 to 78 years. In 17 the therapy produced considerable improvement. The improvement always followed from one to three days after the dehydration. In 5 other patients the effect was no better than that obtained with the older regimen. Two patients showed no improvement, and 4 died. Complicating diseases, in 1 case pneumonia, in several cases hypostatic bronchitis and in many myocardiac defects, were likewise favorably influenced by the dehydrating treatment.

J. A. M. A.

THERAPEUTIC SUCCESS OF THREE DIFFERENT TREATMENTS OF EPIDEMIC MENINGITIS. H. BOEHNCKE, Ztschr. f. Kinderh. **62**:29 (Aug. 9) 1940.

Boehncke compares 44 cases of epidemic meningitis in which serum therapy was employed with 46 cases in which serum and a sulfanilamide preparation were

used. There were 30 fatalities among those in which treatment was with serum, a mortality of 68 per cent. In the 46 cases observed since 1938 in which sulfanilamide preparation was given in addition to the serum, the mortality rate was reduced to 8.6 per cent. Although the two groups represented different periods and the age distribution was slightly different, the author thinks that this does not explain the difference in the mortality rates. The preparations used were sulfanilamide and acetylsulfanilamide. Sulfanilamide was given in the first 20 of the 46 cases and acetylsulfanilamide in the other 26. The author prefers the latter preparation because it can be given in concentrated solution by intravenous, intramuscular or intraspinal injection and because its toxicity is less than that of sulfanilamide. Another advantage of acetylsulfanilamide especially important in meningitis is that it readily passes the cerebrospinal barrier. Acetylsulfanilamide proved more effective. Of the 20 cases in which serum and sulfanilamide was used, 4 had a fatal outcome, whereas of the 26 in which serum plus acetylsulfanilamide was employed there were no fatalities. The author concludes that employment of meningococcus serum plus acetylsulfanilamide is the method of choice in treatment of epidemic meningitis.

J. A. M. A.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

BERNARD J. ALPERS, M.D., *Presiding*

Regular Meeting, Dec. 12, 1941

Migraine with Motor Aphasia, Sensory Aphasia and Abdominal Crises: Report of Cases. DR. A. M. ORNSTEEN.

The sole purpose of this report is to give the younger members of the society the opportunity to hear the patients describe their subjective experiences with their individual types of migraine. The electrical recording of the patient's own description of the features of his attack lends color and emphasis to the clinical symptom complex. The first patient had paroxysmal headache and vomiting from the age of 6 to 12 years. He had no further trouble of this nature until the age of 30; now, for the past year and a half, he has had six attacks of cerebral migraine, the characteristics of which are scintillating scotomas, left-sided headache, nausea and vomiting, paresthesias of the right limbs, the right side of the tongue and the right lower part of the face and motor aphasia.

The second patient, a man, suffers from paroxysmal headache without visual or gastric symptoms but with an interesting form of sensory aphasia with anomia. During the attack he is unable to associate the name of an object with its physical appearance and use. For instance, he knows that P R T (Philadelphia Rapid Transit Company) on the side of a trolley has to do with the streetcar, but he cannot interpret the meaning of "Rapid Transit" in relation to the vehicle. When looking at a fence or a tree he knows what the object is but cannot think of its name and if any one mentions the name, he cannot correlate the name and the object. In other words, he has transient anomia, and, in addition, he is often at a loss for the proper words. When he feels an attack coming on he tells a friend that in the event he does not converse intelligently there should be no concern because it will be over in an hour or two, during which time he usually lies down because of the intense headache.

The third patient, a woman aged 50, for ten or twelve years has been having two types of attacks, one simple migraine and the other abdominal crises. The latter type begins with epigastric pain, gradually increasing in intensity and spreading throughout the abdomen until it reaches the rectal region. She is distressed with cramplike pain, and this is followed by vomiting, which is rather severe. The attack is terminated by a large, copious liquid evacuation. It is interesting to note that her twin brother suffers from attacks of giant urticaria and that her father and 2 other brothers died of coronary disease. This history suggests the possibility of a heredofamilial vascular anlage.

DISCUSSION

DR. S. B. HADDEN: My experience with abdominal migraine is confined to 1 case. I am pleased to learn that Dr. Ornsteen believes that such a condition exists, for in the case in which I made such a diagnosis the patient was studied elsewhere and the examiners informed him they had never heard of such a thing as abdominal migraine. The man gave a history of typical unilateral headache between the ages of 12 and 15 years. At the approximate age of 24 periodic attacks of abdominal pain with vomiting occurred, as a result of which he had had several laparotomies, without relief. The man's mother had typical attacks of migraine, during which a hemianopic field defect developed. The maternal grandmother had a similar type of headache and committed suicide.

The condition is rare and as a rule is not diagnosed unless, as in my case, there is a history of antecedent headache and a strong family history of migraine.

Dr. Ornsteen's second case is an interesting one about which to make neurologic conjectures. The history suggests that the patient at times has anomia, but, in addition, he is unable to appreciate the use of an object that he hears described. The difficulty, I believe, is a disturbance of the conceptual mechanisms—a higher psychic process—and in view of the fact that it occurs in a right-handed patient who has other subjective evidence of a lesion in the right hemisphere, it is probable that the involvement is one of the interhemispheric association pathways. The visual and auditory conceptual mechanisms both appear to be implicated in this instance.

Significance of Deformity of the Sphenoid Fissure in the Roentgenographic Diagnosis of Intracranial Tumors. DR. KARL KORNBLUM and DR. GEORGE R. KENNEDY.

Attention is directed to the value of alterations in the appearance of the sphenoid fissure as a roentgenographic manifestation of an intracranial or intraorbital tumor. Because of the variations in the appearance of this fissure, anatomic and roentgenologic studies were made of a series of normal skulls. As a result of this investigation six distinct types of fissures are described as occurring normally. Special emphasis is placed on the importance of proper roentgenographic technic. A method for showing the sphenoid fissure to its best advantage is also described.

The various types of deformity of the sphenoid fissure are discussed, as well as the particular intracranial and intraorbital tumors commonly producing these changes. Six cases which serve to illustrate various aspects of this subject are reported.

DISCUSSION

DR. R. A. GROFF: Dr. Kornblum and Dr. Kennedy have presented an interesting sign. Many have observed the sphenoid fissure in roentgenograms, but not with the same degree of critical thought the authors have displayed. Their observations seem to me to be helpful in further localization of brain tumors.

Two points have been emphasized: First, the sphenoid fissure does not alter its characteristic normal shape in cases of intracranial growths, particularly those along the sphenoid ridge. Second, the anatomic as well as the clinical observations must be taken into consideration before the roentgenographic changes related to the sphenoid fissure can be considered helpful.

DR. J. C. YASKIN: I should like to ask the authors how they explain the disappearance of landmarks on both sphenoid fissures in cases of certain unilateral tumors. They also mentioned the dilatation and other changes in the sphenoid fissure contralateral to the site of the tumor. Did I misunderstand?

DR. KARL KORNBLUM: Yes, the fissures may be enlarged; they may disappear, depending on the mechanism.

DR. B. J. ALPERS: Was the last case you described, Dr. Kornblum, the one you reported with Dr. Groff in a paper on tumors in the orbital apex similar to tumors of the sphenoid ridge?

DR. KARL KORNBLUM: No, it was not.

DR. B. J. ALPERS: My associates and I have long been interested in this sign that Dr. Kornblum and Dr. Kennedy have pointed out, because we had the advantage of Dr. Kornblum's opinion on roentgenograms of the skull at Jefferson Medical College. I personally have been interested in the possible mechanism of the erosion. I believed, with Dr. Kornblum, until this study crystallized, that the erosion of the sphenoid fissure and the sphenoid ridge was indicative of a local lesion, either in the parasellar or in the suprasellar area—more likely the parasellar. But as Dr. Kornblum pointed out, it may occur with tumors of the cerebral hemisphere.

Some of the cases Dr. Kornblum mentioned are cases that we studied together, particularly one of a meningioma in the parasellar area, in which erosion of the sphenoid fissure appeared on the same side. Despite this, it seems to me that the most important mechanism of production of the erosion is local, for example, pressure from an aneurysm pounding away or the erosive action of an encapsulated tumor, such as a meningioma. At the same time, I think that increased intracranial pressure may operate, with bilateral erosion of the sphenoid ridge, through blocking off of the venous outflow from the orbit and resultant erosion of the sphenoid fissure.

From the standpoint of localization the sign is an important one, and is helpful when there are other evidences of parasellar or suprasellar tumor. But when it is present, and I believe that Dr. Kornblum will agree with this, it is indicative of a large tumor.

When one considers that an expansion of about 2 cm. is required before a pituitary tumor reaches, or at least can produce signs of pressure on, the chiasm, one has some idea how large a tumor must be in order to produce erosion of the sphenoid fissure. Therefore, I should regard this sign as indicative of a large, expanding lesion growing out of the sella or of one that is involving the parasellar region. From that standpoint the sign may have some prognostic significance, for since the tumor is large the possibility of operating on such a growth may not be good. In localization of a lesion of the posterior fossa, it cannot be said that the sign has yet proved of much significance.

Dr. Karl Kornblum: In all but 6 of the cases, that is, in 86 or 88, the lesion was located in such a position that the deformity was probably due to direct pressure, i. e., erosion of the bone. This seems to be an important point; therefore when one observes a bona fide deformity of the sphenoid fissure, it is in the majority of instances indicative of a lesion in the immediate neighborhood.

Dr. Alpers has already given the reason, I believe, that one finds erosion in cases of tumors that are located at a distance. All are familiar with roentgenograms in cases of increased intracranial pressure, and it will be noted that many times the bones are extremely thin and that some thinning occurs in the floor of the anterior and posterior fossae. When one sees such demineralization and thinning of the bone, attributed to increased intracranial pressure, one may also observe that the same process serves to block out the outlines of the sphenoid fissure on either side. If such is the case, the discrepancy noted in the sphenoid fissure may simply be one which partakes of the generalized thinning associated with increased intracranial pressure, and thus will have no localizing value.

In part, this answers the question about hydrocephalus, with which there is associated an increase of intracranial pressure. In the adult there is no chance for widening of the sutures or for expansion of the head, and the mechanism of demineralization and thinning will likewise be operative as an erosion of the sphenoid fissure.

A review of cases of neurologic conditions, exclusive of brain tumor, showed no instances of deformity of the sphenoid fissure unless there was concomitant increase of intracranial pressure.

Dr. Ornsteen asked about the overgrowth that is manifested by increased density, usually of the lesser wing of the sphenoid bone. Such a lesion, to my mind, indicates one of two conditions: either hyperostosis, due to an overlying meningioma, or osteoma. Such increased density is not associated with hyperostosis in any other condition. Of course, one does see benign hyperostosis, which usually occurs in the frontal region. We have at least 1 case in which there is a deformity of the sphenoid fissure. Incidentally, this happens to be unilateral, which I am inclined to believe is part of a hyperostosis frontalis.

The point I wish to emphasize is that this is not a sign that will stand by itself, unless there are other roentgenographic as well as clinical signs. I do not believe the sphenoid fissure is ever pathologically deformed in the absence of clinical manifestations. We have had a number of cases in our series of what appeared to be deformity of the sphenoid fissure without any neurologic signs.

On the basis of a large number of examinations, we have come to accept such distortions of the sphenoid fissure as representing normal anatomic variations.

That there is great variation in this anatomic landmark must be constantly borne in mind by the roentgenologist. We have seen the fissure on one side and a tumor on the other. I remember distinctly a discussion in the neurologic conference at the Graduate Hospital. I insisted that a certain patient had a supratentorial tumor, largely because the sphenoid fissure was deformed. Dr. Schuster expressed the belief that the patient had a tumor of the posterior fossa, which it proved to be. I was relying entirely on my impression that deformity of the sphenoid fissure could not occur unless a tumor was directly pressing on the fissure, which is not true.

Tetanus: The Action of Its Toxin; Prophylaxis and Treatment. Dr. Harris B. Shumacker Jr., Baltimore (by invitation).

Experiments concerning the pathogenesis of tetanus which have been carried out at the Johns Hopkins University in recent years, and which were initiated by the late Dr. John J. Abel, are described. These permit the conclusion that local tetanus is due to the poisoning of peripheral nerves and organs by toxin, that tactile reflex motor tetanus is due to the action of toxin on the motor cells of the central nervous system and that tetanus toxin is distributed throughout the body by the blood vascular system and is not transported to the central nervous system by means of the peripheral nerves. The question of fixation of toxin and of possible alteration in the central nervous system is discussed. Experiments are described in which the intrathecal route was found much more efficacious than the intravenous in the treatment of general tetanus in laboratory animals. The present concept of the treatment of clinical tetanus is stated. Prophylaxis with antitoxin, especially prevention through active immunization with tetanus toxoid, is discussed, and the present status of immunization through toxoid is summarized.

DISCUSSION

Dr. S. B. Hadden: About ten years ago the National Association of Police and Fire Surgeons urged on biologic supply houses the development of methods of active immunization against tetanus. Dr. Wenger, of Mulford Biological Laboratories, became interested, and for a time I had the privilege of working with him in an attempt to develop an active toxin. Groups of police and firemen volunteered, but, unfortunately, immune bodies were not developed satisfactorily from this toxin. I believe that Dr. Shumacker has given the reason; we did not wait sufficiently long after the immunizing injections before beginning the studies of the blood.

This work has since progressed to the point where active immunization against tetanus is of interest not only to the military but to the industrial surgeon. There is little doubt that after this war active immunization against tetanus will be carried out routinely on children and persons in hazardous industries.

Dr. R. L. Masland: In this paper, Dr. Shumacker has criticized the theory that the tetanus toxin is transmitted to the central nervous system through neuronal pathways. I wonder whether the recent work of Bodian and Howe on the spread of poliomyelitis virus through the nervous system does not tend to support such a theory.

I should also be interested in hearing Dr. Shumacker's opinion of the experiments demonstrating the spread of methylthionine chloride (methylene blue) along the nerves.

Dr. G. D. Gammon: Dr. Shumacker, does active immunization protect your animals against tetanus toxin injected into the cord? Also, does active immunization produce antibodies rapidly enough to protect against inoculation of a limb with tetanus toxin?

Dr. B. J. Alpers: I should like to ask how soon in the case of a person who has been actively immunized one must give the additional dose after the development of a wound.

DR. H. B. SHUMACKER, Baltimore: In regard to the passage up the nerves, it was Dr. Abel's feeling and, I am sure, Dr. Elman's, that in most of those experiments in which dye was injected into a nerve the dye had been artificially driven into the central nervous system or the cerebrospinal fluid by force of the injection. If one injected a certain amount of dye very slowly and under very low pressure it would stay within the nerve, whereas if one injected it at the proximal end of the nerve under great pressure one could sometimes demonstrate it in the cerebrospinal fluid or in the spinal cord.

I happen to be rather close to a group who have worked on the spread of the poliomyelitis virus and are just as convinced that this virus does not spread up the nerves as I am that the tetanus toxin does not. They have done experiments of the sort which my associates and I have done with tetanus toxin, in which all the nerves of a limb are severed and virus or toxin is injected into that limb, with development of general tetanus or poliomyelitis just as though the nerves were intact, there being taken into consideration the lessened activity of the limb and, consequently, the decreased venous and lymphatic return. At any rate, the virus is a living, multiplying organism, which tetanus toxin is not.

The remarks that were made about the early experiments on toxoid are particularly interesting to me, because one of the early investigators of this problem gave human beings a single dose of toxoid and immediately discontinued his experiments because he was unable to demonstrate antitoxin in the blood. He suggested at that time, many years ago, that perhaps it was because he had not given doses comparable to those which were given to experimental animals. His is the only report in the literature in which I can find such a suggestion. Every one else accepted Ramón's explanation that the first injection was necessary to "sensitize" the patient so that he would react to subsequent injections by production of antitoxin. My personal feeling, although I have no proof of it, is that there is no difference in the mechanism of man and that of other tetanus-sensitive animals. It is not a question of initial sensitization but simply one of dose, and it is interesting in that respect that, although most investigators are in agreement that a single injection of the usual dose causes no demonstrable antitoxin in man, 3 workers have found appreciable amounts after a single injection. Two of these persons found rather small amounts, and they were dealing with adults. McBride, at Duke University, reported the results of studies on 92 children to whom he had given 1 cc. of tetanus toxoid; of course with small children the amount of toxoid per unit of weight is far greater than in adults. He demonstrated an appreciable amount of antitoxin in all but 2 of 92 children, many of whom had high titers. So I am rather optimistic about the production of a better toxoid which may result in a demonstrable antitoxin titer even with a single dose.

In regard to the question of how soon after a basic course of immunization one should give a subsequent injection of toxoid in case of injury, I can only say that 0.1 unit of antitoxin is almost certainly protective, that a good bit less may possibly be protective and that almost every one is agreed that 0.1 unit of antitoxin is likely to remain in the blood of an actively immunized person for four, five or six months. I should say that after that time one would feel safer if one repeated the dose of toxoid.

In answer to Dr. Gammon's question, at the time we were interested in those studies which led us to offer a theory in explanation of the difference between tetanus-sensitive and tetanus-resistant animals, we felt that the ability of tetanus-resistant animals to prevent in some unknown way the fixation in the central nervous system of a relatively large part of the peripherally introduced toxin also offered an explanation of the mechanism of immunity, both active and passive. That is, in active and passive immunity one of the cardinal achievements is neutralization of toxin before it reaches the central nervous system. Although I cannot give any definite figures, I know from our experiments that an actively immunized monkey, for example, will be immunized against a great many lethal doses of toxin which are introduced intravenously, intramuscularly or subcutaneously, but that the same monkey will succumb to a much smaller amount of toxin if it is introduced into the central nervous system. Consequently, I believe

one of the effective measures manifest in active immunity is the prevention of fixation of toxin within the central nervous system and that perhaps the central nervous system may still be susceptible. I am not sure whether it is just as susceptible as that of the nonimmunized subject.

If a person has not been actively immunized it is not possible at present to bring about active immunity rapidly enough to depend on toxoid for prevention of development of tetanus. Whether or not it will be possible with more potent toxoids I cannot say. But if a person is actively immunized it is safe to depend on the rapid increase in antitoxin titer in response to a repeat dose for the titer is known to reach a high level within a week and to begin to rise in the middle of the first week. In most cases of tetanus the incubation period is at least four or five days, and in a vast majority of them it is a week or longer.

CHICAGO NEUROLOGICAL SOCIETY

ROY R. GRINKER, M.D., *President, in the Chair*

Regular Meeting, Dec. 18, 1941

An Unusual Tumor of the Cerebellum: Report of a Case. DR. PERCIVAL BAILEY and DR. ERIC OLDBERG.

Tumors involving primarily the anterior lobe of the cerebellum are rare. In the case reported here the tumor arose from the leptomeninges over the anterior lobe and destroyed the greater part of the culmen. It was actively invasive and destructive and had the structure of an alveolar sarcoma. The patient, a man aged 23, fell ill abruptly with headache, vomiting and dizziness. A month after the onset he was stuporous, with paresis of both sixth nerves, choked disks, stiff neck, weakness of the left side of the face, a Babinski sign on the left and astereognosis of the left hand. Cerebellar signs of the usual sort were slight. There was no nystagmus and no asynergy of the extremities on voluntary motion. He could not stand and was very weak and ill. He was thought to have a tumor in the right parietal region, and, his condition indicating that a minimum of surgical intervention was advisable, a right osteoplastic exploration was made by one of us (E. O.). No tumor was revealed, but the ventricle was observed to be dilated. Although a decompression was made, the patient obtained no relief and died a few days later.

The clinical symptomatology of the anterior lobe of the cerebellum is unknown, so that tumors of this region cannot at present be localized. The syndrome of the flocculonodular lobe, as demonstrated by the common medulloblastoma of childhood, and the longer known syndrome of the neocerebellar hemisphere, as well as the syndrome produced in animals by the extirpation of the anterior lobe, are discussed. It is urged that a routine search be made for symptoms of cerebellar tumor in clinical cases, to the end that these rare tumors of the anterior lobe may some day be recognized.

DISCUSSION

DR. PAUL C. BUCY: Does Dr. Bailey have any explanation for the fact that the extensor spasticity which follows decerebellation is not persistent but paroxysmal, while that which follows intercollicular decerebration is continuous?

DR. ROY R. GRINKER: I should like to ask Dr. Bailey about Fulton's statement that change in tone is not characteristic of cerebellar lesion but is caused by pressure in the brain stem.

DR. PERCIVAL BAILEY: The occasional occurrence of astereognosis with tumor of the cerebellum has been well established. The explanation offered by Dr. Mackay that the ascending sensory pathways are involved through pressure of the restiform body against the tentorium is probably correct; the pyramidal tract is involved in the same way.

The syndrome of the anterior lobe is discontinuous in these cases. I do not know why. When one stimulates in any way an animal with a lesion of this region, it shows marked exaggeration of symptoms. I suppose that is because the anterior lobe is an inhibitory organ. Alone of the lower animals, the chimpanzee is known to exhibit definite hypotonicity and nystagmus after removal of the cerebellar hemisphere. Perhaps this may also be true of the other higher apes.

Idiopathic Recurrent Thrombophlebitis with Cerebral Venous Thromboses and Acute Subdural Hematoma. Dr. Paul C. Bucy and Dr. Frederick J. Lesemann.

A man aged 37 began to suffer from recurring attacks of thrombophlebitis in his thighs. This persisted on and off for four years. From 1930 to 1941 he was well. On Sept. 18, 1941, at the age of 52, thrombophlebitis developed in the upper portion of the left arm. Three days later he had temporary loss of consciousness. Subsequently he had three more attacks, all associated with marked flushing of the skin, exophthalmos, dilatation of the pupils, rapid feeble pulse, pronounced fall in blood pressure and profuse perspiration. On October 1 he began to complain of headaches. Signs of increased intracranial pressure gradually developed with no localizing manifestations. On October 25 ventriculographic examination disclosed a mass in the right side of the cranial cavity. Exploration revealed this to be a large acute subdural hematoma. Many of the superficial cerebral veins were thrombosed. A decompression was made. The patient rapidly recovered and left the hospital on November 12. He was well when last heard from, on Feb. 27, 1942.

The disturbance of which this man suffered four attacks is interpreted as similar to Penfield's diencephalic autonomic epilepsy. It is thought that the seizures resulted from additional thromboses in the hypothalamic region.

The relation of idiopathic recurrent thrombophlebitis to Buerger's thromboangiitis obliterans is well established. Fortunately, instances of cerebral involvement with this disease are rare. It is thus impossible to offer a valuable prognosis.

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DISCUSSION

Dr. F. J. Lesemann: There is a question in my mind as to why this man, apparently in good health, at the age of 35 suddenly had these repeated attacks of thrombophlebitis, often accompanied by severe cerebral involvement, as manifested by unconsciousness, and then went on to apparent spontaneous recovery. What connection did the attacks have with the thrombosis? Ordinarily noninfective thrombosis of a vein causes little systemic disturbance. Why should this man have had the cerebral manifestations unless the unknown etiologic factor involved something more than merely the cause for local thrombosis?

Dr. A. Earl Walker: For the past six months I have had under observation a patient with much the same symptoms as those exhibited in Dr. Bucy's case. He is a young man, of sedentary occupation, who first had thrombophlebitis in one leg and then severe headache. When I first saw him, some six months ago, he had slight weakness of the right side of the face, tenderness over the left frontal area, but no other neurologic abnormalities. A spinal puncture revealed that the spinal fluid was under a pressure of 270 mm. and contained 27 lymphocytes per cubic millimeter. While the patient was under observation the headaches decreased and the general condition improved. He was discharged from the hospital but suffered several jacksonian epileptic attacks involving the right arm and the right side of the face. For this reason he returned to the hospital.

During his present hospitalization multiple thromboses have developed in the arms and legs and the jugular veins. Both eyes have been so swollen that he has hardly been able to open them. The scrotum has likewise been edematous. In the past three or four weeks the edema of the eyes and scrotum has subsided.

The spinal fluid has on some occasions been fairly normal, but recently the pressure has again been increased and papilledema has developed. Biopsy revealed an organizing thrombus and little inflammatory reaction of the thrombotic lesions and chronic hyperplasia of the lymph nodes of the inguinal region.

This patient's condition corresponds well with the type of recurrent thrombophlebitis, the predominant manifestations of which are in the nervous system.

DR. ROY R. GRINKER: With regard to Dr. Oldberg's question, thrombosis of the longitudinal sinus and of the cortical veins does produce sufficient pressure to cause rupture into the subarachnoid space.

DR. PAUL C. BUCY: I want to thank Dr. Grinker for pointing out that with thrombosis of the cerebral veins and the superior longitudinal sinus, of whatever cause, both intracerebral and extracerebral hemorrhages commonly occur.

Dr. Walker's case brings up problems that I am not able to answer. The number of such cases has not been large enough for one to know what the prognosis is. A patient with this condition may well have further attacks with more severe disability than this man has. On the other hand, recurrent thrombophlebitis involving structures other than the brain ordinarily has a good prognosis. In a few instances the disease has run a more malignant course. Dr. Walker will recall such a case in which the disease spread to the intra-abdominal veins and the man died of mesenteric thrombosis.

A Proposed New Surgical Approach to the Trigeminal Root. DR. HARRY SICHER and DR. ABRAHAM ETTLESON.

The patient is placed in the recumbent position. The exposure is made behind the ear, by a small bone flap or an enlarged burr hole. The dura is opened, and the parietal lobe is retracted to the ridge of the tentorium. A flap is made in the tentorium, one side of which runs parallel with the petrosal sinus, from just below the tentorial ridge for a distance of about 0.5 cm., and the other is directed posteriorly for a short distance, at a right angle to the first incision. The tentorial flap is retracted, thus immediately exposing the isolated root of the trigeminal nerve.

In this approach there are certain advantages and disadvantages. Among the advantages may be mentioned the avoidance of the middle meningeal artery and of traumatizing the gasserian ganglion and the cavernous sinus, which so frequently occurs with the standard subtemporal approach. At this point the motor root lies most medially in the nerve bundle. The principal disadvantage is that the proposed approach is intradural.

Although the procedure has been carefully worked out on anatomic specimens, it has not to date been employed clinically. The authors feel, nevertheless, that it is a feasible surgical approach to the fifth root.

DISCUSSION

DR. A. EARL WALKER: I have had the pleasure during the past year of listening to the three presentations of new procedures for avulsing the posterior root of the trigeminal nerve. At the meeting of the American Academy of Neurological Surgery in Cleveland a year ago, Drs. Herrmann and Wilkins presented a paper in which they described the intradural approach to the posterior root, an incision being made in the dura over Meckel's cavity. This is essentially the second approach which the authors of this evening's paper advocate. Drs. Herrmann and Wilkins expressed the opinion that this method decreased the incidence of facial paralysis.

At the meeting of the academy in November 1942, in San Francisco, Dr. Exum Walker, of Atlanta, Ga., described another approach to the posterior root. He made a small opening just below the lateral sinus and cut the dura over the cerebellum. Then, by making a lumbar puncture, the cerebellum was allowed to fall away from the tentorium, leaving a space of about 1 cm., at the depth of which the eighth and fifth nerves could be seen and sectioned without difficulty.

The third procedure is that presented this evening. The authors discussed it from a strictly theoretic standpoint, but the method is certainly feasible, although the question remains to be determined whether it is preferable to the classic rerogasserian neurectomy.

DR. PERCIVAL BAILEY: According to tradition, this is the approach Sir Victor Horsley used in the operations he first performed for trigeminal neuralgia, and which he abandoned later for the extradural approach of Cushing.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

JAMES B. AYER, M.D., *Presiding*

Regular Meeting, Jan. 15, 1942

Congenital Lethargic Encephalitis: Report of a Probable Case. DR. AUGUSTUS S. ROSE.

A man aged 22 was admitted to the Boston Psychopathic Hospital because of impulsive behavior. He was born in 1919, after a pregnancy in the latter part of which the mother had influenza and lethargic encephalitis. The patient showed retarded development and throughout childhood and adolescence exhibited unpredictable, impulsive and sometimes asocial behavior. Neurologic examination revealed evidence of mild parkinsonism. The mother manifested muscular twitchings and memory disturbances after the delivery, and five years later had petit and grand mal epilepsy. Two years ago a progressive tremor of the right hand developed, and the clinical picture is now one of mild parkinsonism.

The case is presented as one of chronic encephalitis, probably contracted in utero.

DISCUSSION

DR. MADELAINE R. BROWN: During consultation in the mother's case, in 1935, Dr. Lennox was unable to say whether the convulsions were due to idiopathic epilepsy or were secondary to a lesion in the region of the hypothalamus. I myself do not feel certain about it now. I do not remember seeing a patient with parkinsonism and convulsions. Because of the tremendous memory loss that this woman has, she knows nothing about the attacks of epilepsy afterward, and it is hard to get a history of what has happened. I think she has improved a good deal under treatment with phenobarbital. The drug has controlled the grand mal convulsions but not the fainting spells. During the last two years she has received dilantin also and has improved, but the fainting attacks have never been eliminated entirely. My diagnosis was chronic encephalitis with convulsions secondary to a lesion in the region of the substantia nigra and hypothalamus. She has always had abnormal pupils and a Babinski sign on the right, but there was no difficulty in convergence until recently. There now are tremor on the right side, without rigidity, and masklike facies.

DR. WILLIAM L. HOLT, Westborough, Mass.: I should like to tell Dr. Rose about a somewhat similar case, that of a man of about the same age whose disorder was known soon after birth. The history of the mother was the same in that she had a severe illness in the latter part of her pregnancy. The disturbance was called toxemia of pregnancy rather than influenza, but she may have had encephalitis. I associated the child's difficulty in walking, his impulsiveness in behavior and his assaults on other children with congenital encephalitis of toxic or infectious origin. In my opinion, both he and his mother had lethargic encephalitis. The mother does not present as good a history of lethargic encephalitis as the woman in Dr. Rose's case. I have seen her in my office, and she certainly does not show gross evidence of parkinsonism.

DR. JAMES B. AYER: What did von Economo say?

DR. AUGUSTUS S. ROSE: He referred to the occurrence of the disease in infants but did not discuss prenatal infection.

DR. HENRY R. VIETS: This is an interesting report of an extraordinarily rare condition and brings up the question of transmission of a neurotropic virus from person to person. Direct transmission occurs in diseases such as poliomyelitis. Now that something is known about these viruses and how they may be transmitted —in poliomyelitis, for instance, through the feces or by flies—may one not surmise that transmission in Dr. Rose's case was from mother to child after birth, rather than through the placental and uterine circulation?

DR. AUGUSTUS S. ROSE: In regard to the question raised by Dr. Viets, one, of course, cannot be sure how or just when the patient contracted the disease. The cases of Marinesco and Kononowa, furnished pathologic evidence that the disease can pass the placenta. In the more recent case of Schleussing symptoms began at the age of 10 days, which, in the author's opinion, was too early for the disease to have been contracted after birth.

A Survey of Neuropsychiatric Work at the Boston Induction Station.
DR. WILFRED BLOOMBERG and CAPT. ROBERT W. HYDE (by invitation).

The theory behind the setup of army induction boards and the inclusion thereon of neuropsychiatric examiners is discussed. The technic of examination which has been worked out at the Boston station is briefly reviewed. This involves examination of each man by a neuropsychiatrist, who spends an average of six minutes with each recruit and examines about fifty men per day. In an attempt to evaluate the efficacy of this procedure, a comparison of statistics for this station with those for other induction stations in the First Corps area is made.

It is found that the rejection rate for neuropsychiatric disorders at the Boston station is about 50 per cent higher than the average for the First Corps area. It is also found that in a comparable period the disability discharge rate for neuropsychiatric reasons after induction into the army is about 50 per cent lower for men inducted through the Boston station than the average rate for men inducted through other stations in the First Corps area.

It is concluded that the elaborate organization of neuropsychiatric work at the Boston induction station has proved its value and should be continued, and indeed extended when possible to other induction stations.

This paper will be published in full in the July 1942 issue of the *American Journal of Psychiatry*.

DISCUSSION

CAPT. ROBERT W. HYDE: It is interesting to note the difference in the attitude of the neuropsychiatrists toward their work at the induction board and that of the other specialists. From the start, even under the most unfavorable conditions, when examining from 400 to 500 men a day, and with inadequate space, they started the work of research and investigation of their efficiency, when others were too tired even to consider such a thing. That work has continued up to the present. The first investigation was that of Dr. T. J. C. von Storch and Captain Pratt, and it has continued with increasing interest, because now we of the board are able to see some of the results of our mistakes. We are seeing men sent to camp, discharged and returned to civilian life because of mental disorders. We have this check on our efficiency, and it has pleased us because it shows that we have been doing comparatively good work in spite of difficulties.

DR. HARRY SOLOMON: Are too many men rejected? That is a question in which, I take it, the recruiting services are more interested than in whether all are rejected who should be. Has Dr. Bloomberg any figures on rejectees who have been wrongly rejected? Are there more rejections since the local draft board is no longer examining so earnestly?

DR. CHARLES A. MCDONALD, Providence, R. I.: In the last war I was a member of the advisory board. Afterward I examined thousands of veterans.

Diagnoses after the last war were based on the classification of the Veterans Bureau, and not on any psychiatric classification. I rarely encountered a man in whom I could find anything wrong; yet all were getting pensions.

DR. WILFRED BLOOMBERG: My colleagues and I realize that the period is a short one. We are not making any flat-footed statements. We are trying to assess so far as we can the validity of what we are doing, in order to know whether it is worth while to continue with it. As we are organized, all our figures are relative. There are no absolutes. Our only conclusion, if there is any, is in terms of the apparently greater efficiency of our screening process than that of other stations. It is a comparative figure. The final answer will not be available for twenty years, if then.

Are too many men rejected? I do not know and have no way of knowing. I know General Pershing said, "Don't send us any more neurotics." We are told what our criteria should be, and I think that bears on what Dr. McDonald said. We are interested not in making a diagnosis but only in detecting a degree of defect which will make it likely that a man will break down in the service. Our only diagnosis, if it were left to us, would be "constitutionally unfit for army service" or "constitutionally unfit." As to the increase in rejections since the local boards have stopped examining carefully, it is only in the last three or four weeks that we have been getting men without previous examination, and while the rejection rate is higher, we have no figures yet.

Nobody pretends that we are screening out all the men who should be rejected; we only hope that we are eliminating more than would be if we did not have the neuropsychiatric board.

DR. HARRY SOLOMON: Dr. McDonald appeared to be discontented with the work of holding out incompetent, unsuitable draftees. I might say that the congressional act of giving pensions to men is not a function of the Selective Service Board. Their task lies in getting a group of soldiers and sailors who are likely to stand up under the conditions of war. Too many men in the last war broke down at camp after a few days or weeks. In the expeditionary force too many men broke down. Such men are a menace; their spirit is contagious; they affect others and present a grave responsibility. The Canadians now will not object to my mentioning the fact that they took the point of view which Dr. McDonald emphasized. They accepted nearly every one and gave them only six weeks' training; at first they got many derelicts and homosexualists. Homosexualists are not desirable material, particularly if they are of the anxiety-developing or aggressive type.

Pathogenesis of Paralysis Agitans (Parkinson's Disease). DR. CLEMENS E. BENDA and DR. STANLEY COBB.

On the one hundred and twenty-fifth anniversary of James Parkinson's essay on shaking palsy his masterful description is still unsurpassed.

Clinical investigations on Parkinson's disease have confirmed most of his observations and have explained the clinical picture of this disease as an extrapyramidal disorder. The main symptoms which have been added since Parkinson's time are the masklike facies, the disorders of speech, the cogwheel rigidity of the limbs, the fading out of handwriting and other motions, the slowness of reactions and the numerous manifestations of dysfunction of the autonomic nervous system, such as the greasy skin. It is still a matter of argument whether the autonomic disorders are due to involvement of the hypothalamus or are part of the dysfunction caused by a lesion of the substantia nigra, which may play a part in autonomic as well as motor regulation.

The appearance of postencephalitic paralysis agitans has brought unexpected insight into the complex pathology of the extrapyramidal motor disorders. It seems well established that the lower nuclei of the basal ganglia, especially the substantia nigra, are most involved in Parkinson's disease.

It has taken much time and many controversies to establish the main pathologic picture of Parkinson's disease. Proved facts seem to be (*a*) that the substantia

nigra is almost invariably damaged; (*b*) that the lesions are widespread, and not restricted to the substantia nigra, and (*c*) that the pyramidal system is spared.

Our material of 8 cases offers evidence that the substantia nigra is one of the most important sites of lesions in paralysis agitans. In cases of unilateral tremor marked differences in the destruction of the cells of the substantia nigra of the left and of the right side were exhibited, the contralateral side being more involved, while the degeneration of the globus pallidus was of the same extent on the two sides. In all cases in which a complete histologic examination was made it was found that lesions were not restricted to the substantia nigra. The corticostriatal connections were regularly involved, and lesions of the frontal and precentral cortex were evident.

The physiology and pathology of the extrapyramidal system is discussed in order to clarify the nomenclature and to emphasize the difference in the pathologic features of the various extrapyramidal diseases.

Analysis of the parkinsonian tremor reveals that it is not a "resting" tremor, nor is it true hyperkinesis. The tremor is a part of the hypokinetic syndrome and seems to occur because those cortical impulses which are conveyed through the pyramidal tracts reach the end organ while the discharges conveyed through extrapyramidal pathways are out of order. Transmission of the motor nerve impulses is thus reduced and simplified to the primitive pattern of synchronized innervation, alternating in antagonistic groups of muscles. Thus parkinsonian tremor is due to a certain disorganization of the extrapyramidal motor mechanism, causing a new configuration of the paths that remain capable of function.

Our cases, as well as those reported in the literature, indicate that in a large number of instances a condition which is called "idiopathic" is in reality inflammatory disease of the brain. Some of the disturbances are residuals of epidemic encephalitis, but other types of encephalitis may produce the same syndrome. The production of paralysis agitans by syphilis has been reported, and tumor and trauma are known to cause a transient and atypical parkinsonian syndrome.

It is established that paralysis agitans may develop because of arteriosclerotic changes in the brain, but this factor is not as common as one would suspect from the literature. Even in cases in which the pathologist reports arteriosclerotic changes in the other organs, the arteriosclerotic alterations in the cerebral vessels are frequently negligible.

Senile tremor with some stiffness does not justify the diagnosis of paralysis agitans. As a matter of fact, senile changes in the brains of patients with paralysis agitans are rare.

After the various types of symptomatic parkinsonism are discussed, the question remains whether or not all cases of paralysis agitans ought to be considered as representing a "symptomatic" disorder. Many investigators feel that there remains an original group of cases which represent a nosologic entity. Genetic studies have suggested an "abiotrophic," heredodegenerative form of the disease which develops in early life and represents a nosologic entity similar to Wilson's disease and Huntington's chorea. Pathologic studies have so far failed to establish such an entity. The few reports are not worked up well enough to be conclusive. This problem should be investigated further, and only a thorough genetic, clinical and pathologic study of cases of so-called juvenile paralysis agitans will bring about the solution of the question.

The therapy of Parkinson's disease has been conservative until lately, when neurosurgery opened a new approach by attacking the extrapyramidal system directly. It remains to be seen how far this active treatment will be beneficial in management of the various types of paralysis agitans. Our clinicopathologic studies suggest that, taking into consideration the chronic inflammatory character of the changes in many cases and the possibility of toxic agents in others, it is conceivable that a more ingenious medical approach to the disease may succeed in the development of a more hopeful therapy.

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DISCUSSION

DR. STANLEY COBB: Dr. Benda has worked on this material for years and has amassed some extremely interesting histologic data.

The lesions in these new cases were widespread, but I believe that the emphasis on the substantia nigra (especially in the French school) is an exaggeration of the facts. One gets the impression that if all the cases reported in the literature had been as carefully worked up as these of Dr. Benda's, the disease would in almost all instances have been diagnosed as encephalitis.

Finally, the theory of the pathogenesis of the tremor of paralysis agitans is new and is, we believe, based on certain physiologic and pathologic observations.

DR. KURT GOLDSTEIN: It has been interesting to hear such an excellent review of the achievements in a field of neurology in which one has had the opportunity to follow developments. In my experience the lesions of the substantia nigra are more pronounced in the encephalitic process than in real parkinsonism. Is that in accordance with Dr. Benda's observations? Another question comes to mind: I have seen a number of cases in which Parkinson's disease has occurred in 2 brothers. This suggests that one has to reckon with degenerative factors in this disease. I should like to know whether Dr. Benda has observed such cases.

DR. CLEMENS E. BENDA: It is rather hard to answer these questions. In regard to the localization of the lesions, I think one ought to accept as one of the results of research of the last twenty years that destruction of the cells of the substantia nigra is found in paralysis agitans as well as in postencephalitic parkinsonism. Recently some one tried to make a pathologic distinction between the site of the lesions in the substantia nigra observed in paralysis agitans and that observed in parkinsonism, but I do not think that such a distinction can be made.

As to Dr. Goldstein's question whether in cases with marked tremor the lesions are more severe in the lentiform nucleus and whether in cases with extreme rigidity the lesions are especially noticeable in the substantia nigra, I should say that our experience is rather in the other direction. I feel that rigidity is somewhat related to lesions in the globus pallidus, while lesions in that region are not sufficient to explain the occurrence of tremor.

We called attention to the problem of degenerative paralysis agitans as a disease entity. As pathologist I might say there is not enough evidence of a heredodegenerative disease; those cases formerly described as instances of juvenile paralysis agitans were not sufficiently well studied and the disease probably was not paralysis agitans at all.

I feel that a clinical differential diagnosis of paralysis agitans and parkinsonism is possible, but in general the clinical data are too poor for one to reach a definite conclusion. I suggest that in any case of paralysis agitans a thorough study of other members of the family be made.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

RAYMOND W. WAGGONER, M.D., *President, in the Chair*

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General and Cerebral Lesions Associated with Feebleminded. DR. S. STEPHEN BOHN, Detroit.

The pathologic changes observed in the body organs and brains of 221 feebleminded patients who died at the Lapeer State Home and Training School over an eleven year period are reviewed. Only cases with complete autopsy reports are included in the study. Of this series of patients, 122 (55.2 per cent) were

males and 99 (44.8 per cent) females. The great majority, 208 (94.1 per cent), were white, and the remainder, except for 1 American Indian, were Negroes. Death occurred most frequently between the ages of 1 and 50 years.

It was found that the lungs and pleura were most frequently involved, followed by the vascular system and then by the genitourinary, the gastrointestinal and the hepatic system, in close order (table 1). In only 20 patients (9 per cent) were no pathologic changes observed. A summary of the pathologic changes in the body organs (table 2) shows that the respiratory system was most frequently involved and that such respiratory diseases as pneumonia and tuberculosis were most common. Congenital anomalies of the body organs were observed in only 6 patients.

The pathologic conditions in the brains of these patients consisted predominantly of congenital malformations, the most frequent of these being pachygyria, micrencephalia, microgyria, neuronal changes, atrophies, poor differentiation of cortical layers, increase in glia and heterotopias. The cerebral lesions could be classified both on a macroscopic and on a microscopic basis. Congenital mal-

TABLE 1.—*Pathologic Changes in Body Organs*

System	No. of Cases
Respiratory	172
Vascular	62
Genitourinary	42
Gastrointestinal	37
Hepatic	36
Miscellaneous	35
No pathologic change	20

TABLE 2.—*Pathologic Changes in Body Organs Classified According to Disease*

Disease	No. of Cases
Pneumonia (all types)	86
Tuberculosis (various organs)	79
Heart disease	50
Carcinoma	10
Congenital anomalies	6

formations were much more frequent than were infection, degeneration, neoplasms or cerebrovascular accidents.

Thirteen (5.9 per cent) of the patients studied had positive serologic reactions for syphilis. Six of these showed the aforementioned cerebral malformations and disturbances in cytoarchitecture. It is believed that these 6 patients would have been feebleminded in the absence of syphilis.

DISCUSSION

DR. A. A. STRAUSS, Northville, Mich.: I was impressed by Dr. Bohn's frequent observation of congenital malformations in the brains of feebleminded persons. I have stressed the fact that in persons with the higher grades of mental deficiency an organic defect, if it is present, is usually due to injury or inflammatory disease. This opinion has been endorsed by many other investigators. I am surprised to note that Dr. Bohn found malformations more frequent than injuries in the feebleminded. I hope that he may be able later to show how patients with congenital malformations of the brain and those with defects of the brain due to injury may be differentiated clinically.

DR. HENRY A. LUCE, Detroit: I should like to ask Dr. Bohn to differentiate between the causes of death in the general population and those present in the

group. He stated that diseases of the respiratory tract were the major cause of death among the feebleminded, with cardiovascular diseases second. That is similar to what is noted in the general population. Is there any significant difference in the two groups?

DR. S. STEPHEN BOHN, Detroit: I also have been impressed by the similarity in the causes of death in the feebleminded group and those in the general population. It seemed to me, however, that the incidence of respiratory disease was exceedingly high in this series of patients, higher than has been found in the general population.

Studies of the Spinal Fluid Pressure in Cases of Injury to the Head. DR. E. S. GURDJIAN, DR. JOHN E. WEBSTER and DR. CARL J. SPRUNK, Detroit.

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DISCUSSION

DR. JOHN E. WEBSTER, Detroit: It has been my opportunity to conduct experiments on the cerebrospinal fluid pressure on dogs that had sustained injuries to the head. The animals were not anesthetized at the time the experiments were carried out. The normal cerebrospinal fluid pressure in dogs is between 100 and 145 mm. of water. The injection of isotonic fluid in normal dogs in quantities of from 40 to 60 cc. per kilogram within one hour was followed by a moderate increase in cerebrospinal fluid pressure. The final mean increase in pressure was less than 50 mm. The intravenous administration of a 50 per cent solution of dextrose in normal dogs produced a fall in pressure, which was followed by a return to the initial level. A secondary rise was observed in only 1 instance, in which a sucrose solution had been used.

Thirty dogs were given severe head injuries while under anesthesia. The anesthesia was then discontinued, and the observations were made. In 80 per cent of the dogs the cerebrospinal fluid pressure was below 200 mm.; in 3 it was above 300 mm., and in the highest it was 450 mm. The effects of administration of isotonic fluid and of 50 per cent solution of dextrose were similar to those noted in the uninjured animals. There was no correlation between the fluid intake and the cerebrospinal fluid pressure.

Clinical Implications of Psychosomatic Medicine. DR. LOUIS A. SCHWARTZ, Detroit.

Clinicians working entirely with organic illnesses are handicapped by distortion produced by psychic factors. Laboratory tests and clinical records may be altered by the psychic component of illness. Operations that seemed exigent on clinical study may be rendered unnecessary by treatment of the psychic manifestations.

Of the last 300 cases studied in the diagnostic service at Harper Hospital, Detroit, a primary psychiatric diagnosis was made in 53 and a secondary psychiatric diagnosis in 58, or in a total of 111. There were, in addition, 53 cases in which the illness was considered to be somatic, with obvious functional or psychogenic elements, and 69 cases of metabolic or endocrinologic disorders. In a total of 233 cases, or 78 per cent, therefore, definite psychosomatic abnormalities were present.

The psychosomatic approach permits a scope of examination which gives one a deeper understanding of the patient's illness and aids in the evaluation of the underlying personality problem.

DISCUSSION

DR. HUGO A. FREUND, Detroit: The psychiatrist plays an important role in furnishing the final diagnosis and the recommendations for treatment. Internists realize how often emotional states of all kinds predispose to or actually usher in a series of symptoms that ultimately shape themselves into a pattern or syndrome, which becomes a reality. It is also known that an organic lesion, a degenerative

condition, trauma or other state may set up a chain of subjective complaints that ultimately affect remote parts of the body. These may apparently be totally unrelated to the original focus. The eagerness of the psychiatrist to find a psychosomatic explanation must not tempt him by circuitous reasoning to seek other than apparent and plausible causes for illness.

I recognize the contribution that analyses such as these of Dr. Schwartz offer. They are of inestimable assistance in the individual case, and they give promise of providing a better understanding of the patient's problems. The internist has simple methods of approach. He gathers factual material from the history and the physical, roentgenographic and laboratory examinations. He correlates the results, compares the physiologic processes and reaches a logical conclusion. He would like, for example, psychobiologic data that offer proof of pain. He would like evidence of the degree of pain, a measure of unpleasant sensation or understanding of the difference between pain as it is felt in the mucous membrane, the depths of the abdomen and on the body surface. To what degree does a somatic sensation produce a psychic response?

I am quite ready to admit the value of the psychosomatic approach to the study of any case, but not until the organic factors have been completely evaluated. The psychologic manifestations should not be permitted to obscure facts obtained in the physical examination. They should be accepted as a part of the picture only in so far as they give expression to or illuminate the obscure and the intangible functional variations.

DR. LEO H. BARTEMEIER, Detroit: Dr. Schwartz's excellent paper represents the first extensive study in psychosomatic medicine in Michigan. This orientation represents the most adequate approach to the understanding of the illnesses of people because it insists that knowledge of the personality of the sufferer is a necessary part of the diagnostic study. I was glad that Dr. Schwartz emphasized the importance of the method of taking the history. If a sick person can only be allowed to tell the story of his illness in his own language, with as little interruption as possible, one can gain a far better appreciation of the nature of his disorder than by the question and answer procedure which has too long characterized clinical medicine. The procedures which Dr. Schwartz has outlined impress all with the fact, which has often been neglected, that the illness and the person are indivisible.

DR. LOWELL S. SELLING, Detroit: I should like to add just one word. When one is working with behavior rather than with physical disorders one sees the effect of the physical disorder on the behavior. No one can measure behavior directly, but I believe that it is measurable. Two children may have identical illnesses, but the action of environment, of society and of the child's own personality in relation to the illness bring out entirely different forms of behavior.

DR. R. GORDON BRAIN, Flint, Mich.: There is some lack of agreement between the psychiatrist's and the internist's conception of the term disease. Mutual understanding would effect a gain in teamwork and would enhance the value of consultation with one or the other. This is especially true in regard to the so-called functional disorders, many of which will find their way into the domain of organic disease through the development of new laboratory methods.

The common ground of the internist and the psychiatrist should be in the appreciation by both of the relation between morphology and the tendencies toward physical disorder and personality or behavior patterns.

Book Reviews

A History of Medical Psychology. By Gregory Zilboorg, in collaboration with George W. Henry. Price $5. Pp. 606. New York: W. W. Norton & Co., 1941.

Gregory Zilboorg has brought together in this volume a large mass of historical and biographic material, the fruit of much reading and reflection, vivified by a passionately crusading spirit. All earnest students of human nature will surely welcome this impressive attempt to bring into a certain coherent relationship the intellectual and humanitarian efforts of many generations of contributors in a segment of medical history hitherto much neglected. Not all, however, will be so appreciative of the interpretations offered. For example, the author's most strikingly recurrent theme is the struggle between priest and physician for possession of the field here called medical psychology. This interpretation lends itself well to a dramatic mode of presentation, but the emphasis on this militant theme seems to the reviewer excessive. Surely not all the physicians enlisted here under the banner of conquest could have been motivated primarily by the militant and partisan urge "to capture the field of mental disease." It seems more probable that a number of them, like many of the medical men of one's living acquaintance, were chiefly concerned in gaining a competent understanding of the patients brought to them.

The appreciative and careful reader will note, however, that this book is not set forth arrogantly as *the* history, but is offered more modestly as *a* history, and the author makes clear in the prologue his intention of avoiding a mere compilation of historical facts. "If proper enjoyment and enlightenment are to be derived from the reading and writing of history, one must mobilize, not anesthetize, one's feeling, revitalize all strivings, even weaknesses and passions" (page 18). In fulfilment of this avowal, one is offered here a gorgeous pageant of historical portraits, animated by the learned author's dramatic talents and imbued with his own passionate and partisan devotion to his profession.

Much attention is given to the Middle Ages and the Renaissance—almost 200 vividly written pages. Here one finds stirring biographies of three of the author's four outstanding heroes—Johann Weyer, humane physician; Juan Luis Vives, sensitive delineator of psychodynamic subtleties, and Theophrastus Bombastus von Hohenheim (Paracelsus).

In dealing with the more modern period (since Pinel), the frankly partisan evaluations presented will doubtless arouse dissent. For example, one wonders why a history of medical psychology should ignore Kraepelin's contributions to the testing of psychologic functions. The whole development of psychologic testing is left out. Readers have cause to be grateful, however, for the appreciative presentation of a number of lesser known figures—Daquin, Ideler, Feuchtersleben and Groos, for example—and also the Semelaignes, to whom the reader may well feel especially thankful for their contributions toward the creation of this book.

The outstanding hero of this history is, of course, Sigmund Freud. In view of the recurrent theme of militancy, there is doubtless a deep significance in the author's selection of Ludwig Jekels' obituary remarks: "As to love, did not Freud's work reclaim for mankind the right to love? Did he not elevate love to the level of a legitimate, vital and natural factor of life? This he saw fit to do at a time when love was given recognition only by poets and was more generally regarded as a play of the imagination, a whim or a mood."

And so, from this deeply moving historical pageant, one may gather not only facts but an inspiring appreciation that those whose professional labors have enlightened the understanding of man, in some of his least lovely modes of reaction,

have been imbued with a warmly individualized humanistic spirit. This humanistic spirit has shown itself as a benevolently humanitarian attitude toward the afflicted and, also, perhaps more significantly, as a profoundly considerate respect toward all that is human in man—sane or "insane," "possessed" or free. It is in this sense that the reviewer welcomes Zilboorg's delineation of the history of medical psychology, including its most modern developments, as a product of the Renaissance.

George Henry contributes the last two chapters, one on organic mental disease and one on mental hospitals. These are more matter-of-fact in manner and substance than the earlier portions. There is a noteworthy section on dementia paralytica.

There are 19 pages of illustrations, mostly portraits, and a useful 16 page index.

The Clinical Application of the Rorschach Test. By Ruth Bochner, M.A., and Florence Halpern, M.A. Price, $3.00. Pp. x + 216. New York: Grune and Stratton, Inc., 1942.

The authors of this small volume purporting to describe the clinical application of the Rorschach method devote the first of the book to a general discussion of the procedure and scoring of the Rorschach test. Although they state that their material is essentially derived from the literature, they neglect to include in their bibliography the two papers of Klopfer, "The Technique of the Rorschach Administration" and "Theory and Technique of the Rorschach Interpretation," from which most of their material might have been derived. This omission is surprising since some of the Klopfer theories have never been published elsewhere. Their handling of this material tends, unfortunately, toward oversimplification, and they are apparently unaware of certain changes which have been made since these articles were first published, some years ago. In addition, the authors themselves do not seem at all clear in their discussion of the more difficult problems. Their discussion of the M : Sum C ratio tends to be confused, and they contradict themselves concerning the meaning of the basic ratios on three consecutive pages. It requires more skill and experience than the average psychiatrist possesses to interpret these pages, 52, 53 and 54.

The major difficulties with the work appear, however, when the authors approach the clinical field. Although the book purports to be a study of clinical application, it deals only with mental deficiency, neuroses, schizophrenia and "organic" disorders. Apparently the authors have had no experience with the affective psychosis or else consider this broad aspect of psychopathology as negligible.

The clinical data given in the last half of the book are scant and filled with errors. An example of some of the misstatements is the interpretation of the value of popular responses of the mentally defective subject. Apparently the authors are unfamiliar with the work of Beck (the major investigator in this field), who stressed the significance of popular responses in indicating the ability of the defective person to get along in institutions. It is amusing to note in this connection that the sample record given for a mentally defective person has a high percentage of popular responses, in contradistinction to the authors' previous assertion, and that their records substantiate Beck's findings even though their theoretic statements do not.

Concerning the rest of the theoretic discussion dealing with clinical entities, there is little to say except for enumeration of the frequent errors. The authors do not seem to be aware that there are no true pathognomonic signs of schizophrenia or that their "neurotic indicators" are not only nonspecific but unsubstantiated by any type of research. Their failure to recognize variation in the quality of the performance in cases of damage to the brain is a serious oversight. The greatest drawback to the book, however, is its misleading oversimplification. The authors would have one believe that the technic is an easy one and that diagnoses can be made by simply scoring a record and then looking up the listed interpretation. Workers in the field are in complete agreement on the fact that there is no specific pattern or response for any psychopathic deviation. The Rorschach method gives only a personality pattern which clinicians must evaluate and interpret.

A number of case records have been included, but the paucity of clinical material and the superficiality of the histories destroy any usefulness they might possess.

In conclusion, one can only say that the large number of errata, the poor printing, the incomplete bibliography and the lack of an index make the physical structure of the book seem as unfinished as the content.

The Principles of Neurological Surgery. By Loyal Davis, Professor of Surgery and Chairman of the Division of Surgery, Northwestern University Medical School, Chicago. Second edition, enlarged and thoroughly revised. Price, $7. Pp. 503, with 154 engravings, 298 illustrations and 5 colored plates. Philadelphia: Lea and Febiger, 1942.

The revision, enlargement and new dress of the second edition of Dr. Davis' book make it a much more valuable production than the first edition, and the freshness of style and illustration is gratifying. It avowedly is written not for the neurosurgeon but for the general practitioner, as a source of facts regarding neurosurgical problems and the results to be expected from neurosurgical intervention. However, in its scope it is really compendial, and its content of useful and valuable detailed information is presented with simplicity and clarity, fitting its purpose well. Of great advantage is the generic treatment and origin of material, in contrast to the other publications in this field, which have dealt too exclusively with the experiences of an individual author or clinic. This avoidance of emphasis on personal experience and of arbitrary treatment of controversial subjects is complemented by the use of abundant original illustrations and useful diagrams.

Inevitably, the subject of tumors is elaborated, and the clinical and pathologic data detailed in this chapter represent an excellent summary of matter seldom found in a book of this scope. Trauma and infection are likewise well covered. However, it is from items of lesser proportion, but of great practical usefulness in diagnosis and after-treatment, which the general reader will find throughout the book that he may derive the greater value. Pain, especially the treatment of trigeminal neuralgia, hypertension, hydrocephalus and epiletiform seizures are all dispassionately and thoroughly treated, so that the general practitioner may be informed as to the relative brilliance of results which may be expected in the surgical treatment of the respective diseases.

Methods of Treatment in Postencephalitic Parkinsonism. By Henry D. von Witzleben. Price $2.75. Pp. 135. New York: Grune & Stratton, Inc., 1942.

This is a comprehensive review of all the methods of treatment that have been utilized in the past in the management of postencephalitic parkinsonism. Most of them are of only historical interest. It includes a rather extensive bibliography on the subject. A chapter on diagnosis and differential diagnosis should provide interesting reading for the clinician, though the reviewer disagrees with some of the criteria offered as differentiating true paralysis agitans from the postencephalitic parkinsonian syndrome. A chapter on pathology would have been a welcome addition.

The author indicates that he regards the Bulgarian treatment as far superior to all other forms previously used. Though he states that the best results with the Bulgarian treatment are obtained only in combination with physical exercises, he omits any reference to what would happen to patients who received the benefits of similar physical exercises while taking some of the other medicinal preparations. It is unfortunate that the preparation recommended is not available in this country.

Physicians will find in this small volume information that should aid them materially in the management of these difficult cases.